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NEUROFIBROMA AND NEUROFIBROSARCOMA OF PERIPHERAL NERVES

UNASSOCIATED WITH RECKLINGHAUSEN'S DISEASE: A REPORT OF TWENTY-FIVE CASES

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Neoplasms of the peripheral nervous system are relatively uncommon, but their occasional occurrence and variable prognosis warrant their study with a view to standardizing, as far as possible, the methods of treatment. New growths of the cutaneous nerves and nerve trunks have long been recognized when they occur in the form of Recklinghausen's disease, and the problems relevant to this condition have been well recorded in the past and current literature. Less attention has been paid, however, to the isolated tumors of nerves when unaccompanied by generalized neurofibromatosis, and it is our purpose in this communication to record our experiences with this type of growth. The twenty-five cases herewith presented illustrate the various pathologic changes and indicate the sites at which neurofibroma and neurofibrosarcoma of the peripheral nerves are commonly encountered. While the distal portions of the cranial nerves do not strictly belong to the "peripheral nerves," we have taken the liberty of including one case in which there was a tumor of the face presumably arising from the middle branch of the fifth cranial nerve and two cases in which there were tumors arising from the vagus nerve in the neck. We have excluded consideration of the related benign tumors of the sheath of the acoustic nerve and of the spinal cord roots which have been fully treated in the monographs of Cushing [1] and Elsberg,[2] respectively. We have also excluded neoplasms of the sympathetic nervous system, which fall into a special group necessitating separate discussion.

From the Departments of Surgery and Pathology of the Peter Bent Brigham Hospital and the Harvard Medical School.

1. Cushing, H.: Tumors of the Nervus Acusticus, Philadelphia, W. B. Saunders Company, 1917.

2. Elsberg, C. A.: Tumors of the Spinal Cord, New York, Paul B. Hoeber, Inc., 1925.

PATHOLOGIC STRUCTURE

Normal Nerve Sheaths.—It is well to preface a discussion of the tumors of the nerve sheath by briefly reviewing the structures which normally comprise the neural envelops. The nerve fiber, if it is a medullated one, is surrounded by a thin layer of myelin which, supposedly, is concerned with the insulation of the nerve pathway, and encircling a myelinated or unmyelinated fiber there is a supporting coat, which is called the neurilemma or the sheath of Schwann. This sheath, which modern writers generally agree is of ectodermal origin (Masson [3]), is interrupted at short, rather regular intervals of a millimeter or less at the nodes of Ranvier. An aggregation of such covered fibers is encased by a perineurium which holds the group together as a bundle. A number of these fasciculi are in turn surrounded by the epineurium to constitute the nerve proper. Peripheral nerve fibers, as well as the fibers of their integuments, have a finely wavy character as contrasted to those of the brain and spinal cord, and theoretically this waviness protects the nerve from injury by allowing it to stretch during movements of a limb or viscus.

Neurofibroma.—From the sheath of Schwann there arises a benign tumor known as a neurofibroma, schwannoma, neurilemoma or perineural fibroblastoma. The terms perineural fibroblastoma (Mallory,[4] Penfield [5]) and neurilemoma (Stout [6]) have been proposed in order to separate this tumor from that form which occurs in Recklinghausen's disease. In this communication, however, we continue to apply the term neurofibroma to all of the benign tumors of the nerve sheaths, whether or not they are associated with Recklinghausen's disease, but we realize that some authors employ it only for the generalized type. Whether the isolated growth takes origin from the neurilemma, perineurium or epineurium is difficult to determine, but probably all three may give rise to the neoplasm under consideration. There have been heated discussions concerning which of the nerve investments is responsible for the development of such a growth, but we do not find the arguments on either side entirely convincing, and hence we do not wish to enter into the vexed problem of ectodermal or mesodermal origin of this

3. Masson, P.: Experimental and Spontaneous Schwannomas (Peripheral Gliomas), Am. J. Path. **8**:367, 1932.

4. Mallory, F. B.: The Type Cell of the So-Called Dural Endothelioma, J. M. Research **4**:349, 1920.

5. Penfield, W.: The Encapsulated Tumors of the Nervous System, Surg., Gynec. & Obst. **45**:178, 1927; Tumors of the Sheaths of the Nervous System, in Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 955.

6. Stout, A. P.: The Peripheral Manifestations of the Specific Nerve Sheath Tumor (Neurilemoma), Am. J. Cancer **24**:751, 1935.

tumor. In any event, its essential character is that of a connective tissue growth, differing from the ordinary fibroma of other organs in several respects, as presently described. Slow growth characterizes this neoplasm, and the gradually expanding fusiform or rounded mass becomes well demarcated from the surrounding soft tissues. As enlargement proceeds, the nerve is not incorporated into the tumor but is pushed to one side or is expanded. The latter characteristic is often important if one desires to remove a neurofibroma and yet maintain the continuity and function of the nerve trunk. Grossly, such a neoplasm is encapsulated and may be peeled away from the nerve which courses along one edge or surface. The external surface is gray or yellowish gray. Degeneration is common, and cystic change may be so extensive that the mass consists of little more than a shell, filled with clear or slightly cloudy, watery or mucinous fluid and traversed by a few remaining threads or bands of tissue (fig. 21 *B*). This transition may be so extensive as to obscure the original character of the growth. Degenerative changes appear to be more common in the tumors which arise in the neck but are also seen in those originating from nerves of the extremities.

The microscopic picture identifies a neurofibroma and is the same as that presented by the well known acoustic neurinoma. The connective tissue fibrils of the neurofibroma occur as long, wavy strands which coalesce into bundles of varying size and form interlacing bands and whorls (figs. 22 and 32). The cells may deposit little or no intercellular substance but usually elaborate collagen in considerable quantities. Collagenous bundles may be hyalinized. The nuclei are narrow, elongated, pointed, hyperchromatic and of a mature type. Mitotic figures are rarely seen. Of particular significance is the arrangement of the cell nuclei in parallel rows, "like nuclei on parade," each being closely packed against neighboring ones. Not all neurofibromas present this feature as strikingly as is illustrated in figure 19, but some degree of this configuration is usually encountered. Blood vessels are not numerous but may be rather large, often appearing as blood sinusoids. Axis-cylinders are found only where the mass is attached to the nerve trunk or where nerve fibers are carried passively into the peripheral portions of the tumor. Degenerative change is common, and this finding often helps one to make the diagnosis. Loss of cell structure, accumulation of interstitial fluid and myxomatous changes appear, and hence there may be a variation from a high cellularity to a loose-textured growth (fig. 3). Commonly, there are foamy phagocytic cells, either scattered in small groups (fig. 29) or accumulated in larger numbers in areas of cystic degeneration. Stains for fat, such as scarlet red, show the lipoid character of the débris contained in these cells.

Malignant Neurofibroma.—In the following series of cases we encountered three specimens which had a somewhat more rapid rate

of growth than that of the ordinary neurofibroma, and yet the degree of malignancy was not sufficient to warrant a diagnosis of neurofibrosarcoma. The histologic picture was rather similar to that presented by benign neurofibroma, but several features evinced a more rapidly growing tumor (fig. 24). The cytoplasm of the cells was more abundant, and the individual fibrils were not as long. The nuclei were shorter and more plump, had less chromatin and were more vesicular in appearance. Occasional nucleoli and rare mitotic figures were encountered. We have hesitated to designate these as sarcomas, for metastases did not occur. There was, however, a strong tendency to local recurrence and even to massive regional extension if they were not completely excised. The term malignant neurofibroma is a poor one, but we have employed it in three cases to indicate a rapidity of growth which is between that of the neurofibroma and that of the neurofibrosarcoma. Such a tumor was seen in case 22, and while there were no metastases such as might be expected from invasion of blood vessels, still there was extensive slow growth over a period of thirteen years, which eventually led to death. In case 19 it was impossible to remove one of these neoplasms surgically, and we have reason to believe that it may ultimately prove fatal to the patient. In case 18 this rather rapid type of growth was again encountered, but in this instance there was clean removal of the mass and the adjacent nerve trunk, and we entertain the belief that this patient will have no recurrence.

Neurofibrosarcoma (Neurogenic Sarcoma).—This tumor, which has previously been studied by Quick and Cutler,[7] Stewart and Copeland [8] and Stout,[9] also arises from the connective tissue coverings of the nerve fibers and fasciculi. It may arise secondarily in a previously existing benign neurofibroma, as is illustrated by case 4. More often, however, rapid growth is evident from the first appearance of the mass (cases 7 and 10). When the tumor is exposed at operation, its malignant nature may be evident by the absence of a capsule, by its infiltrative properties and by the presence of regional extensions of metastases. Not infrequently, however, a well defined capsule is observed, and regional tissue may show no evidence of invasion. In this case the operator is led to believe that he is dealing with a benign lesion. This is particularly prone to occur when there is secondary degeneration in the central part of a previously existing neurofibroma. Hence the clinical history of

7. Quick, D., and Cutler, Max: Neurogenic Sarcoma, Ann. Surg. **86**:810, 1927.

8. Stewart, F. W., and Copeland, M. M.: Neurogenic Sarcoma, Am. J. Cancer **15**:1235, 1931.

9. Stout, A. P.: The Malignant Tumors of the Peripheral Nerves, Am. J. Cancer **25**:1, 1935.

recent active enlargement may be more important to the surgeon than the gross findings at the operating table.

These sarcomas present a variable picture. If they have arisen in previously existing benign tumors, some areas will show evidence of slow growth, such as capsule formation, but other portions are more indicative of malignancy. There may be adhesions to surrounding muscle or other soft tissue, and externally the grayish or grayish red surface is irregular, roughened and hemorrhagic. The cut surface is granular, soft and often friable. Areas of hemorrhage are common.

Microscopically, evidence of rapid growth is shown by the high cellularity, the variation in size of cells, the formation of giant cells and the presence of mitotic figures (figs. 10 and 15). The individual cells are of younger type, possess abundant but poorly outlined cytoplasm, have shorter cell processes and stain irregularly. If some areas of less rapid growth are present, there will be changes similar to those presented by a neurofibroma, such as the formation of bands of elongated wavy cells in bundles and whorls with some palisading of nuclei. One is often not fortunate enough to find the latter changes, and histologically it may be impossible to do more than make a diagnosis of fibrosarcoma, relying for the final diagnosis of nerve tumor on the gross picture of origin from a nerve trunk.

(*Recklinghausen's Disease.*—For purposes of comparison, the histologic picture in generalized neurofibromatosis must be briefly mentioned. The widespread nodular involvement of the cutaneous and larger nerves, the laxity of the skin and the cutaneous pigmentation are well known. A high hereditary factor and a tendency to malignant degeneration are often encountered. The condition may widely affect the extremities, body, neck or head but is occasionally confined to one region, such as the face or trunk. Coincidentally, there may be involvement of thoracic or abdominal viscera, sympathetic nerves or meninges. The swellings of the nerve trunk are rounded or fusiform and quite irregular in size or shape. The condition is probably something more than a neoplasm in the usual connotation of the term, and possibly represents some congenital or inherited tendency to malformation of the nerve. Histologically, there is a distinct difference from the ordinary neurofibroma, for intermixed with the connective tissue overgrowth in generalized neurofibromatosis there is a diffuse and rich supply of nerve fibers of either medullated or nonmedullated types.)

DISTRIBUTION OF TUMORS

The statement has occasionally been made that these tumors may arise from nerves in any part of the body, but a closer analysis of cases shows that they are found commonly in certain areas, that in others they are rare and that in several places they have never been reported.

Stout[6] has made a study of benign tumors of the nerve sheaths (neurilemoma), including his own cases and those reported in the literature. Figure 1, a composite chart, shows the distribution of tumors in Stout's cases and the distribution of the reported cervical neurofibromas of Mayo and Barber,[10] and also of our twenty benign lesions. The tendency of these growths to appear in selected regions makes it advisable to discuss the various sites separately.

Extremities.—Since the longest courses of peripheral nerves lie in the extremities, it is not surprising that these neoplasms are most numerous in the arms and legs. In the arms they may occur along any portion of the major nerve trunks but appear to be somewhat more com-

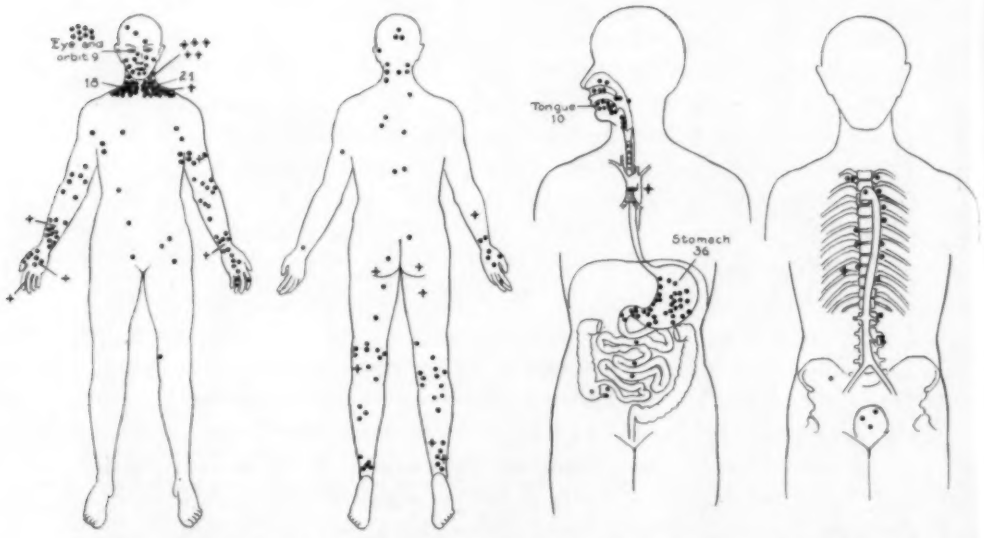

Fig. 1.—Distribution of benign tumors of the sheaths of peripheral nerves. (After Stout.) In addition to the tumors in the cases reported and collected by Stout, the cervical neurofibromas of Mayo and Barber are charted. Our twenty personally observed benign neurofibromas are indicated by crosses.

mon on the median or ulnar nerves at or just above the wrist. They may be found also along the smaller nerve branches of the hands and fingers. Since the major nerves course along the flexor surfaces of the arms and legs, it is not surprising that most of these growths occur on the anterior aspect of the arms and the posterior portions of the legs. The sciatic nerve gives rise to some of the growths in the lower extremity, but the popliteal space and the malleolar regions are common sites. The larger growths occur on the sciatic nerve in the middle third or the upper

10. Mayo, C. W., and Barber, K. W.: Cervical Neurofibroma, Surg., Gynec. & Obst. **59**:671, 1934.

third of the thigh, but smaller ones are often found along the branches of the tibial or the peroneal nerves. The feet rarely give rise to these neoplasms, but we have seen two such examples which are not included in the present series. Peers [11] has recorded a case in which a neurogenic sarcoma arose within the shaft of the ulna.

Neck.—The neck, with its multiplicity of cranial nerves, sympathetic nerves and branches of the brachial plexus, is one of the favorite regions for the development of tumors of the nerve sheaths, and in the presence of a mass in the neck of an adult the possibility of a neurofibroma must be strongly considered. Of the various regional trunks, the cervical sympathetic or a spinal nerve root is probably the most frequently involved, but the vagus, the spinal accessory and hypoglossal nerve (Friedman and Eisenberg [12]) have all been found to be attached to such a growth. Not infrequently, however, it is impossible to tell at the operating table the exact origin of the mass, for the depth of the wound or the obscured position on the under-side of the tumor makes identification of the nerve difficult. In two of our patients we were unable to ascertain the nerve involved, and in a third case we could do little more than infer that the mass was attached to one of the anterior roots of the cervical plexus. Mayo and Barber [10] recorded seventeen examples of cervical neurofibroma, exclusive of those arising in the brachial plexus, and our series includes five such cases. The brachial plexus is responsible for two additional neoplasms in our patients, one arising from the posterior cord and the other from the lateral cord.

Face.—Neurofibroma may be encountered occasionally on the face, the branches of the fifth nerve being most commonly affected. While such a growth may involve only the extracranial tissues, there are a few examples of extension upward through the foramen ovale or rotundum into the cranial vault, or the site of origin may be just at one of the cranial foramina and growth proceed both intracranially and extracranially. This results in a so-called "dumb-bell" tumor, the narrow area representing that part lying in the bony canal. In case 19 a cystic, malignant neurofibroma apparently arose from the second division of the trigeminal nerve, for there was an external bulge low in the temporal fossa, with extension into the orbit and also downward through the pterygopalatine fossa into the soft palate.

Mouth, Pharynx and Larynx.—Ten neurofibromas have been reported in the tongue and sublingual regions, occurring in all parts of the tongue

11. Peers, J. H.: Primary Intramedullary Neurogenic Sarcoma of the Ulna, Am. J. Path. **10**:811, 1934.

12. Friedman, L., and Eisenberg, A. A.: Neurofibroma of the Hypoglossal Nerve, Ann. Surg. **101**:834, 1935.

from its tip to the base. Several specimens have been removed from the hard palate. Rare examples of isolated neurofibroma have been reported in the pharynx. In Figi's [13] case 1 the mass projected into the posterolateral wall of the pharynx and displaced the tonsil inward toward the midline. The mass, when removed, was 3 cm. in diameter. The nerve from which it arose was not known for certainty, the patient exhibiting no disability after the surgical removal. Three cases have been recorded in which the tumor occurred in the aryepiglottic folds of the larynx (Vail [14]).

Thorax.—The intercostal or phrenic nerves may give rise to a neurofibroma in the thorax, which often attains a considerable size. The benignity of the tumor makes surgical removal a most satisfying procedure, and one who is familiar with operations on the thoracic wall and in the cavities of the chest has little difficulty in completely enucleating such a growth. In one instance (case 20) a neurofibroma 6 cm. in diameter lay between the left parietal pleura and the great vessels of the heart. Keller and Callender [15] recorded a somewhat similar case, but with the tumor lower down, between the pericardium and the left lung. An example of neurofibroma of an intercostal nerve is seen in case 21, in which instance the mass was 12 cm. in diameter, was well encapsulated and was attached to the eighth intercostal nerve, from which it bulged into the pleural cavity. The relative softness of the lungs or other intrathoracic structures often allows one of these neoplasms to expand readily and assume a great size. Harrington [16] reported fourteen cases of mediastinal or intrathoracic perineural fibroblastoma, and his success in treating these lesions again emphasizes the desirability of recognizing such benign growths and attempting surgical extirpation. Of forty-six various intrathoracic tumors removed at operation, this author classified fourteen of them as of nerve sheath origin, and ten of these occurred in the posterior mediastinum. (The presence of a neurofibroma in the posterior mediastinum and in the neck may lead to a dumb-bell-shaped tumor which passes through into the spinal canal. The subject of the so-called hour-glass tumors of the spine has been fully treated by Heuer [17]).

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13. Figi, F. A.: Solitary Neurofibroma of the Pharynx, Arch. Otolaryng. **17**: 386 (March) 1933.

14. Vail, H. H.: Schwannoma of the Larynx, Ann. Otol., Rhin. & Laryng. **42**: 476, 1933.

15. Keller, W. L., and Callender, G. R.: Neurofibroma Arising on the Pericardial Pleura, Ann. Surg. **92**:666, 1930.

16. Harrington, S. W.: Surgical Treatment in Fourteen Cases of Mediastinal or Intrathoracic Perineural Fibroblastoma, J. Thoracic Surg. **3**:590, 1934.

17. Heuer, G. J.: The So-Called Hour Glass Tumors of the Spine, Arch. Surg. **18**:935 (April) 1929.

Abdominal Cavity.—The abdominal cavity occasionally contains a neoplasm of the sort under discussion; our series, however, does not include an example of this. The recorded cases reveal the stomach as the most commonly involved viscus and Stout has accepted the growths in thirty-five cases as being truly tumors of the nerve sheaths. Case [18] described a neurofibroma, 6 cm. in diameter, on the posterior wall of the stomach. In the Cabot [19] case 18283, one of these benign growths, 12 cm. in diameter, projected inward from the posterior wall of the stomach. Three or four have been found in the small intestine and one in the cecum, but no case has been reported of such a tumor in the colon or the rectum which was considered authentic. There are isolated reports of these growths appearing along the retroperitoneal tissues.

Skin.—For the purpose of completeness, mention is made of the small nonencapsulated neurofibroma of the skin. Lesions of this type have relatively little importance but must be included in a discussion of tumors of the nerve sheaths. They are small, varying from 5 to 6 mm. to somewhat more than 1 cm. in diameter and from 3 to 5 mm. in thickness. They arise in the corium, do not possess a well developed capsule and are usually removed with the diagnosis of fibroma of the skin. The histologic features, however, are similar to those of the larger tumors of the nerve sheaths seen elsewhere. These small cutaneous lesions have appeared in multiple locations on the surface of the body, often on the back, chest or abdomen, frequently on the extremities and rarely in the neck, but not, in our experience, on the head. We have encountered ten of these cutaneous lesions, but include only two for purposes of illustration.

AGE AND SEX DISTRIBUTION

The benign or malignant tumors of the nerve sheaths are largely encountered in early or middle adult life. They have been found in childhood but are more often seen in the third, fourth or fifth decades. Approximately two thirds of our patients were between the ages of 20 and 50 years, this distribution roughly corresponding to that found in the literature.

In regard to the occurrence of the benign and malignant tumors in males and females, there is no greater tendency for them to occur more commonly in either sex. Thirteen of our patients were men, and twelve were women.

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18. Case, J. T.: Three Cases of Neuroma: Cirsoid Neuroma of Face, Neurofibroma of Stomach, Posterior Nerve Neurofibroma, Am. J. Surg. **8**:648, 1930.

19. Unusual Cause of Hematemesis (Neurofibroma of Stomach), Cabot Case 18283, New England J. Med. **207**:91, 1932.

SYMPTOMS AND SIGNS

The frequency with which these tumors are incorrectly diagnosed preoperatively indicates that few characteristic findings are exhibited by them. There are, however, several general symptoms or signs which are associated with these growths as they occur in various locations on the body. The most common complaint is that of a local swelling, and with the slowly growing neurofibroma this may be present over a period of many years and show only slight progression during that time. Tumors of ten or fifteen years' duration or even longer are not infrequent. Contrary to this, a short duration, of from several months to a year, and rapid augmentation in size are the rule in a neurofibrosarcoma. The overall dimensions of the growth have no prognostic value regarding its benignity or malignancy. The size of the local mass may vary greatly, as can be gleaned by reference to the tabulated list of cases. The smallest lesions were little more than pea-sized swellings along the nerve, while the largest were from 12 to 14 cm. in diameter. The large proportion of these were firm and hard, but the tendency to cystic degeneration must be remembered, and when this occurs transillumination may be demonstrated. In case 16, even when well exposed at operation, the cystic structure was thought to be probably a branchial cleft cyst, and it was not until microscopic examination of the few remaining trabeculae within the cyst that the correct diagnosis was established. The direction of the mobility of the mass may give a clue concerning the attachment to a nerve, for it can be easily moved from side to side, but it is harder to displace it longitudinally along the course of the nerve. Of course, if the growth is a malignant one, it may be well bound down to the surrounding structures. The sarcoma does not metastasize by lymphatics but rather tends to invade blood vessels; hence the absence of involvement of the regional lymph node does not rule out a diagnosis of a malignant growth. In cases in which the presence of sarcoma is suspected, early roentgenograms of the lung may be of assistance in reaching a proper diagnosis and in withholding useless surgical intervention, since pulmonary metastases occur early.

When situated in the mediastinum or the thoracic cage, the local mass often reaches such proportions as to interfere with the surrounding vital structures and thus give rise to symptoms relating to partial obstruction of the venae cavae, the respiratory passages or the esophagus. With a tumor of the hour-glass variety, the outstanding symptoms may be referable to pressure on the spinal cord. In the pharynx or larynx, obstruction of the respiratory tract or difficulty in phonation are the usual symptoms. In the stomach there is little to distinguish such a growth from other benign ones. In this location the tumor is often so small as to be of little importance, but it may reach such proportions

that it is palpable through the abdominal wall. If the growth projects into the stomach it may obstruct the lumen or ulcerate and produce severe hemorrhage.

The incidence of pain is variable, so much so that it cannot be greatly relied on for diagnostic importance. Pain may be of two sorts. First, it may be present in the mass itself, though this is by no means a constant feature. Secondly, the pain may be referred along the nerve to which the tumor is attached. When this radiation is encountered, it may be continuous or may be elicited only when pressure is applied externally on the tumor or when the limb or part is placed in such a position that the neoplasm is compressed by the neighboring tissues. Thus, in case 18 there was pain referred to the forearm and hand when the arm was so moved that the clavicle impinged against a tumor of the brachial plexus. This patient could also elicit the referred pain in the hand by making digital pressure in the supraclavicular fossa. It is well to emphasize again, however, that pain may be absent.

Contrary to what one might expect, paresthesia, hypesthesia, anesthesia or motor paralysis is not commonly encountered along the distribution of the nerve involved by a benign growth. This is due to the fact that the nerve trunk is usually pushed to one side or is so expanded against the soft, surrounding tissues that there is little or no disturbance in the function of the nerve. In contrast to this, malignant neural tumors are more prone to produce sensory or motor disturbances, for they tend to infiltrate the nerve proper and to destroy its fibers by local pressure. In short, then, persistent motor or sensory disturbance favors diagnosis of a malignant, rather than of a benign, lesion.

TREATMENT

The treatment of these growths is surgical, and radiation therapy has little place except possibly as a palliative measure in the terminal stages of neurofibrosarcoma. Local irradiation therapy, either by radium or by roentgen rays, has been almost universally disappointing.

In the surgical treatment of the neurofibroma, two methods of excision are available. By one, the tumor may be shelled out or peeled away from the nerve, leaving the shredded but functionally intact nerve unsevered. By the alternative method, the entire structure is excised, the nerve being transsected on either side of the mass, and the divided nerve is then repaired by end to end suture. There are several factors which influence the choice between these two methods. First, the type of nerve involved is of considerable importance. A small branch, particularly if it is only sensory, may be divided with impunity, whereas one hesitates to divide a large trunk, such as the sciatic nerve, if it can be avoided. Secondly, the involvement of a mixed nerve tends to militate against its division by the surgeon, for restoration of function may

not be as complete as is the case when a purely sensory or purely motor nerve is divided and sutured. Finally, the obviously benign growth may be shelled out from its nerve without hesitation, but if there is any question as to undue rate of growth (such as a malignant neurofibroma) the patient should be given the benefit of the doubt, and the mass and adjacent nerve trunks should be completely and cleanly excised. The latter consideration should be stressed, for while older teachings emphasized the preservation of the nerve, we have come to believe that more radical removal of a portion of the adjacent nerve trunk may be the only method of preventing recurrence. Indeed, we are convinced that in case 18, one of a tumor of the brachial plexus, this course has been well justified. Certainly, this malignant neurofibroma could not have been cleanly removed from the ensheathing nerve, and local recurrence would have occurred. Suspecting the possible rapid growth, we removed the entire mass and nerve trunk. There has been complete restoration of function in the arm, and in three years there has been no evidence of recurrence. We [20] have discussed these operative considerations more fully in a separate publication.

The preceding paragraph deals with the local removal of tumors having a slow or moderate rate of growth. In the highly malignant forms, however, early amputation of the extremity may be a life-saving measure, if performed before metastases have occurred. One should act exactly as one does when dealing with periosteal sarcoma of bone. Amputation should be proposed only when the roentgenogram does not reveal pulmonary metastases, and finally the removal of an arm or leg must be justified by establishing the diagnosis of malignancy on pathologic examination. Such study can be rapidly performed by frozen section preparations and amputation decided on and executed immediately if the findings demand it. We feel reasonably certain that amputation at the first operation in case 4 would have given a chance for complete removal of all of the sarcomatous tissue in this patient.

REPORT OF CASES [21]

The following series of twenty-five personally observed cases includes twenty examples of benign neurofibroma occurring in various parts of the body, as follows: arm, five; leg, five; neck, six; mediastinum and thoracic cage, two, and skin, two. Several of the lesions from the neck showed marked cystic degeneration, and one from the peroneal nerve was also largely cystic. Malignant neurofibroma was encountered three times, once in the subcapsular region, once on the

20. Cutler, E. C., and Gross, R. E.: The Surgical Treatment of Tumors of the Peripheral Nerves, Ann. Surg. **104**:436 (Sept.) 1936.

21. Dr. Harvey Cushing, Dr. John Homans and Dr. David Cheever gave us permission to include case 8, case 16 and cases 5, 17 and 20.

face and once in the brachial plexus. Neurofibrosarcoma was seen twice on the sciatic nerve and once on the median nerve. The tumor on the median nerve developed in a previously existing benign neurofibroma which had been present for twenty years, but the two sarcomas of the leg showed evidence of rapid growth from their first appearances.

Surgical extirpation was attempted in all of our cases, with but two exceptions. In case 10, one of an extensive sarcoma of the thigh, only partial removal was done in an effort to relieve the local discomfort. In case 19 the deeply rooted growth in the temporal and pterygopalatine fossae defied surgical removal; only small fragments could be resected, and the remaining cystic portion was swabbed out with a sclerosing fluid.[22] In the remaining twenty-three cases local excision was performed in each instance, the usual procedure being to shell the mass away from its nerve trunk. In only two instances were major nerve trunks completely divided during operative procedure. In case 13 the left vagus was severed (and not sutured), with resulting permanent hoarseness. In case 18 the completely divided posterior cord of the brachial plexus was resutured, and the resulting loss of function of the radial and axillary nerves has subsequently been fully restored by regeneration of the nerve.

In none of our cases of benign neurofibroma has there been evidence of recurrence, the patients being followed over periods ranging from several months to nineteen years. Of the three patients with malignant neurofibroma, one died of the disease thirteen years after operation, one had a local recurrence within six months and one has been followed three years without recurrence, the last patient being the only one of the three who underwent complete extirpation at operation. Of the three patients with neurofibrosarcoma, all died within one year with extensive pulmonary metastases. The various cases are summarized in the table, and brief case reports are appended.

Case 1.—A. C., a 30 year old woman, was first seen on Feb. 6, 1932, complaining of a localized, oval, nonpainful swelling on the flexor surface of the left wrist, which had gradually increased in size over a period of two years. Examination showed a firm, elongated, nontender mass, 5 cm. long and 1.5 cm. in diameter, toward the lateral aspect of the volar surface of the wrist. There was slight hypesthesia at the tip of the index finger.

Operation.—A hard nodular tumor was exposed, which lay on and was attached to the median nerve (fig. 2). This mass was removed and was dissected away from the nerve trunk, injuring only a few of the nerve fibers.

22. A modification of Carnoy's fluid, after Zollinger and Moritz (Effects of Necrobiotic Agents on the Walls of Cysts Experimentally Produced in the Brains of Dogs, Arch. Neurol. & Psychiat. **28**:1046 [Nov.] 1932). The composition is absolute alcohol, 6 cc.; chloroform, 3 cc.; glacial acetic acid, 1 cc., and ferric chloride, 1 Gm.

*Data in Twenty-Five Cases of Neoplasm of the Peripheral Nervous System**

Case	Sex Age	Type of Tumor	Size and Weight of Tumor	Nerve Involved and Location	Preoperative Duration, Years	Result
			Arms			
1	F 30	Neurofibroma	4.5 x 1.7 x 1.3 cm.	Median, wrist	2	Not followed
2	M 81	Neurofibroma	2 x 1.5 x 1 cm.	Ulna, wrist	7	Not followed
3	F 65	Neurofibroma	3 x 2.5 x 1.5 cm.	Median, cutaneous, palm (?)	10	No recurrence in 12 years
4	M 56	Neurofibrosarcoma	18.5 x 15 x 13 cm.	Median, upper part of arm	20; recent rapid growth	Died in 1 year; metastases
5	F 70	Neurofibroma	2 x 1.5 x 1 cm.	Digital, finger	..	.....
6	M 22	Neurofibroma	4.5 cm. long; 1.8 cm. in diameter	Posterior branch of ulna, forearm	1	No recurrence in 12 years
			Legs			
7	F 32	Neurofibrosarcoma	10 x 9 x 6 cm.	Sciatic	1	Died in 1 year; metastases
8	M 42	Neurofibroma	3 cm. long, 1.5 cm. in diameter	Common peroneal, knee	¾	No recurrence in 19 years
9	M 48	Neurofibroma	15.5 x 7 x 5 cm.	Superficial peroneal, ankle	10	No recurrence in 5 years
10	M 74	Neurofibrosarcoma	18 x 12 x 10 cm. 827 Gm.	Sciatic	¾	Died in 1 year; metastases
11	F 40	Neurofibroma	1 x 0.9 x 0.6 cm.	Posterior tibial, ankle	3	.....
6	M 22	Neurofibroma	8 x 5.5 x 5.5 cm. 122 Gm.	Sciatic	5	No recurrence in 12 years
			Neck			
12	M 19	Neurofibroma	4.5 cm. in diameter	?	3	Not followed
13	M 74	Neurofibroma	6 x 4 x 3 cm. 32 Gm.	Left vagus	5	No recurrence in 5 years; hoarseness produced by section of vagus nerve
14	M 38	Neurofibroma	10.5 x 7 x 6 cm. 253 Gm.	Vagus	15	No recurrence in 5 years
15	F 70	Neurofibroma	8 x 5 x 4.5 cm. 75 Gm.	?	10	No recurrence in 3½ years
16	F 66	Neurofibroma	6 x 3.5 x 2.5 cm.	Anterior root of a cervical nerve (?)	3	No recurrence in 6 months
			Brachial Plexus			
17	F 36	Neurofibroma	2.5 cm. in diameter	Lateral cord	8	Not followed
18	M 23	Malignant neurofibroma	4.7 cm. long; 2.4 cm. in diameter	Posterior cord	1	No recurrence in 3 years
			Face			
19	F 32	Malignant neurofibroma	4.5 cm. in diameter (?)	Maxillary branch of trigeminal (?)	7	Recurrence in 6 months (?)
			Mediastinum and Thoracic Wall			
20	M 35	Neurofibroma	6 x 5.5 x 4 cm.	? Left phrenic, mediastinum	10	No recurrence in 17 years
21	F 27	Neurofibroma	8.8 x 7.6 x 7.8 cm. 326 Gm.	8th intercostal, right	5	No recurrence in 3 years
			Back and Perineum			
22	F 30	Malignant neurofibroma	7 x 2.5 x 2 cm.	Long subscapular, beneath scapula (?)	1¾	Recurrence in 6 months; regional and thoracic extensions until death 14 years later
23	F 41	Neurofibroma	Five nodules; largest, 3 x 1.5 x 0.8 cm.	Perineal nerve, perineum	7	No recurrence in 13 years
			Skin			
24	M 32	Neurofibroma	1.5 cm. in diameter; 1.2 cm. thick	Cutaneous nerve, thigh	6	.....
25	M 33	Neurofibroma	5 mm. in diameter	Cutaneous nerve, arm	..	.....

* Surgical removal was employed in each case.

Result.—After operation there were slight tingling and numbness on the flexor aspect of the tip of the index finger as well as along the lateral border of this finger. The patient was followed for only one month after operation.

Pathologic Examination.—The firm, white, nodular and encapsulated structure measured 4.5 cm. in length, 1.7 cm. in width and 1.3 cm. in thickness. The cut surfaces presented faint, white, linear markings or streaks against a faintly grayish white background.

The microscopic picture was typical of that presented by a neurofibroma, with a loose-textured growth of low cellularity. The cells were long, and wavy and of mature type and had formed an abundant collagen. Moderate palisading of nuclei was present.

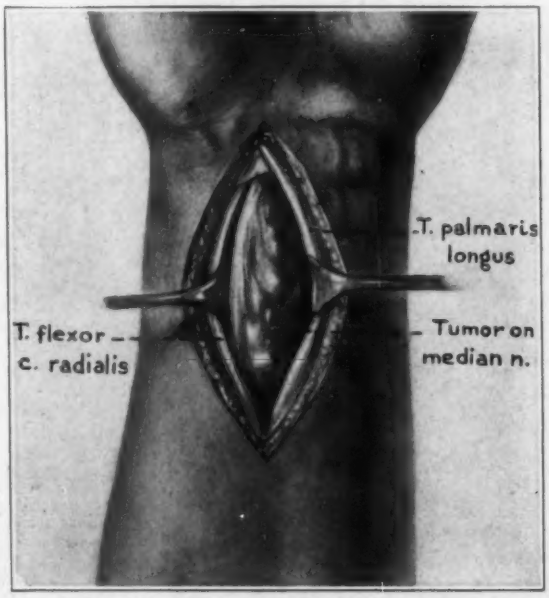

Fig. 2 (case 1).—A lobulated neurofibroma arising from the median nerve. At operation the mass was dissected away from the nerve, leaving the trunk intact.

Case 2.—H. M., an 81 year old man, entered the hospital on Oct. 8, 1920, for treatment of a small mass on the right wrist, which had been present for seven years. Pain in the wrist was a prominent symptom, and there was radiation of this pain down into the palm of the hand. There was a rather firm, tender mass on the ulnar side of the flexor aspect of the right wrist. This seemed to be deep in the tissues, and while freely movable it was apparently adherent to some of the underlying structures.

Operation.—On operation the mass was found to be incorporated in the substance of the ulnar nerve sheath, most of the fibers of which could be seen running along the posterior wall of the tumor. These were carefully dissected away, and finally the whole tumor shelled out easily, leaving the nerve essentially intact.

Result.—Complete relief from pain was obtained. After operation there was slight diminution in sensation over the ulnar distribution of the little finger and the

ring finger. Abduction and adduction of the fingers were accomplished slowly and with difficulty. The patient was lost track of one month after operation.

Pathologic Examination.—The tumor consisted of a smooth, firm, glistening, encapsulated growth measuring 2 by 1.5 by 1 cm. The cut surface was moist and gray.

Microscopic examination showed a typical neurofibroma. Long wavy cells appeared, with interlacing bundles and whorl formations. Many nuclei showed definite palisading. Many areas had a loose-textured myxomatous structure of low cellularity, but these were intermingled with zones of more cellular, compact tissue (fig. 3). In a few portions of the tumor there were occasional large mononuclear phagocytes, laden with lipoid material.

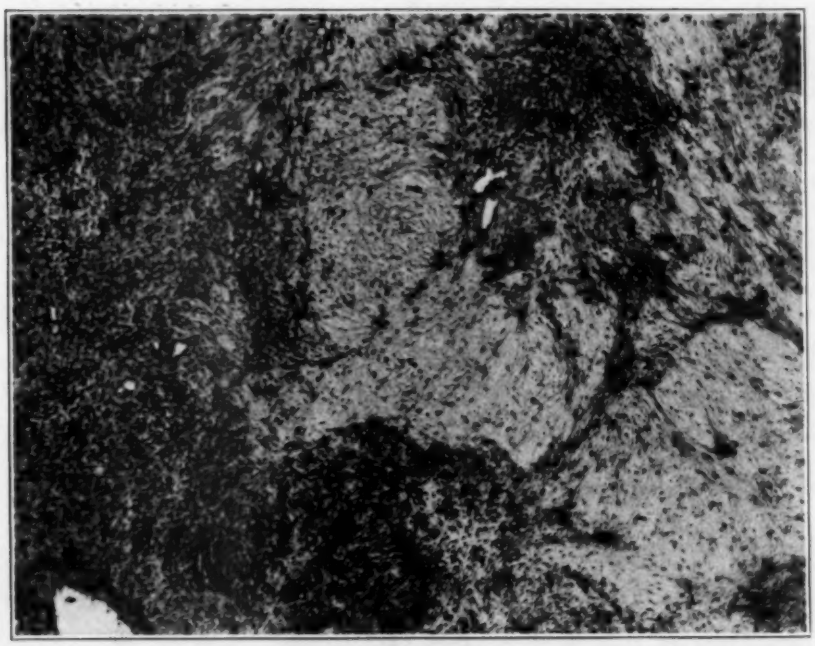

Fig. 3 (case 2).—Low power photomicrograph (× 60) of a benign neurofibroma (from the wrist), showing the great variability in cellularity. Note the more compact tissue toward the left and the loose-textured, reticular substance in the center and toward the right.

Case 3.—M. B., a 65 year old woman, was seen on Jan. 15, 1923, complaining of a lump on her hand which had been present for ten years. This had gradually grown larger, but had given no symptoms except for the inconvenience caused by having it on the palm. Examination showed a subcutaneous palmar mass, which was nontender and about the size of an English walnut.

Operation.—The mass was easily removed, being apparently attached only to the palmar fascia. (It probably arose from one of the cutaneous twigs of the median nerve.)

Result.—The patient has been followed until 1935, during which time there has been no recurrence.

Pathologic Examination.—The specimen consisted of a small pinkish gray, well encapsulated tumor, measuring 3 by 2.5 by 1.5 cm. which, on section, had a variegated appearance. Some areas were grayish white and glistening, while others were deep red and soft and contained considerable blood clot.

Microscopic examination showed, intimately attached to the dense palmar fascia, a typical neurofibroma, many areas of which were undergoing cystic degeneration. The better preserved, wavy fibrillary connective tissue had an abundant intercellular substance. The long spindle cells were arranged in bundles, which ran in various interlacing fasciculi, and the nuclei appeared in palisade arrangements. No mitoses were found.

CASE 4.—F. H., a 56 year old man, entered the hospital on May 27, 1931, for treatment of a nonpainful swelling of the upper part of the right arm which had been present for about twenty years. The slowly growing mass had produced little inconvenience for many years, but during the past five months it had more than doubled its size. Examination showed a large, rounded, firm swelling on the anteromedial aspect of the upper part of the arm, coursing over which were many greatly dilated veins (fig. 4 *A*). The mass was warm and had the appearance of a

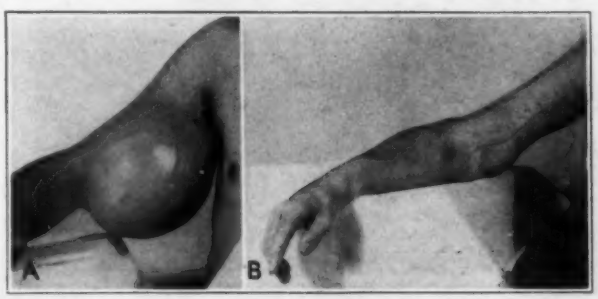

Fig. 4 (case 4).—*A*, a photograph (May 28, 1931) of a tumor of the median nerve which had been present for twenty years and had doubled its size in the past five months. *B*, a photograph after local removal of the tumor.

rapidly growing tumor, yet it was smooth and apparently within a capsule. There were no axillary or pulmonary metastases. Muscles of the fingers and wrist seemed weak, but there were no areas of anesthesia.

Operation.—On operation the upper end of the lesion was seen to spring from the median nerve, which thinned out over the capsule of the tumor. The mass was dissected away from the median nerve, but portions of the brachial artery and veins had to be removed because they were surrounded by tumor. Circulation in the right arm was adequately maintained by collateral vessels. There was no postoperative change in the motor or sensory functions of the right arm. Figure 4 *B* shows the condition of the arm ten days after operation.

Pathologic Examination.—The largely encapsulated tumor weighed 2,200 Gm. and had an ovoid, fairly uniform contour, measuring 18.5 by 15 by 13 cm. (fig. 5). The cut surface was mottled yellowish pink and was crossed by interlacing strands and broad bundles of white and yellowish tissue. In the center and about the periphery of one pole there were irregular zones of gelatinous softening and hemorrhage (fig. 6).

Fig. 5 (case 4).—External view of the tumor of the median nerve.

Fig. 6 (case 4).—Cut surface of the tumor of the median nerve. (From *Ann. Surg.* **104**:436 [Sept.] 1936.)

Microscopic examination showed rather higher cellularity than is usually seen in a neurofibroma. The general picture was one of elongated cells with mature hyperchromatic, long nuclei, the cells occurring in long interlacing and whorled fasciculi. Palisading of nuclei was seen in many places. In some zones the tumor had a loose-textured appearance, and there was evidence of cellular and cystic degeneration. There were some features which would mark this as a malignant type of growth, but these were overlooked at the time. In many regions, particularly where the cellularity was high, the nuclei were broader, more rounded and more immature in appearance, presenting considerable variation in size, shape and staining qualities. The cell processes in these zones were also shorter than those seen in the more slowly growing areas. No mitotic figures were encountered, and the diagnosis of neurofibroma was made. It is unfortunate that additional material is not available for a check-up examination, for it is almost certain that additional blocks from other portions of the growth would establish the presence of malignancy.

Second Entry (Oct. 31).—During the four months since previous discharge from the hospital, a recurrent mass had developed over the entire upper part of the right arm (fig. 7), and there was marked edema below the elbow. There was also a nodule in the left pulmonary field, visible by roentgen examination, which was believed to represent a metastatic tumor. As the arm was useless and was certainly going to cause great distress, amputation was performed in spite of the presence of pulmonary metastases.

Result.—Roentgenograms of the chest in April 1932 showed extensive involvement of the lungs by metastatic tumor, and the upper half of the left lung field was completely obliterated (fig. 8). Seven intensive treatments with high voltage roentgen rays were given over the chest, with little relief. The patient died in May 1932. Permission for autopsy was not obtained. We are convinced that this patient should have had more radical treatment at the first operation. An incision into the mass at the operating table would have excluded hemorrhage or cystic degeneration as the cause of its great increase in size. Amputation should then have been performed immediately.

Second Pathologic Examination.—Over the anterior and medial lower two thirds of the humerus lay a large, irregular tumor, consisting of four quite well separated portions (fig. 9). The median nerve could be traced through the upper portion of the tumor down to this site of former operation, where the nerve frayed out and was lost. The portions of neoplasm measured 11 by 11 by 10 cm., 11 by 9 by 10 cm., 7 by 6 by 3 cm., and 11 by 8 by 3 cm., respectively. The median nerve emerged from the inferior aspect of the large distal tumor and proceeded on the normal course into the forearm. All of the masses appeared to be fairly well encapsulated, and no direct extension into adjacent structures could be demonstrated. On cut section the various nodules were very friable and grayish pink. As a whole they were quite soft and of homogeneous structure, except for the central portions, which were rather necrotic.

The microscopic picture was that of a highly cellular, very malignant, rapidly growing fibrosarcoma (fig. 10). While there was some interlacing of bundles and whorl formation, it would be difficult to say that this was a tumor of the nerve sheath had it not been previously known that it arose in a neurofibroma and was attached to the nerve trunk. The nuclei were all large and vesicular in appearance and had a finely divided and well dispersed chromatin material. The nuclei varied considerably in size and particularly in staining reaction. One or two nucleoli were often seen. Mitotic figures were extremely numerous, and multipolar

Fig. 7 (case 4).—Recurrent neurofibrosarcoma of the median nerve, photographed four and one-half months after figure 4 *B*.

Fig. 8 (case 4).—Roentgenogram of the chest (April 1932) showing extensive pulmonary metastases from the neurofibrosarcoma of the median nerve.

Fig. 9 (case 4).—The recurrent neurofibrosarcoma of the median nerve after removal. The size of the tumor mass can be compared to the humeral shaft seen in the right lower portion of the photograph.

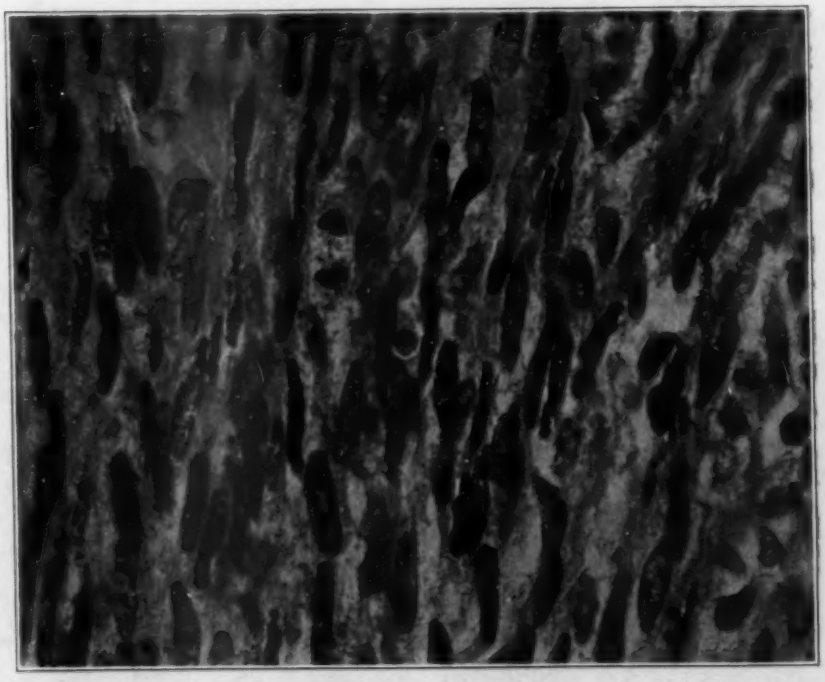

Fig. 10 (case 4).—Photomicrograph (× 700) of the recurrent neurofibrosarcoma shown in figure 9. The nuclei vary in size, shape, staining reaction and chromatin content. There are cytoplasmic outlines and short fibrillary processes. Two mitotic figures are shown in the field.

mitoses were occasionally encountered. Cytoplasms of the cells were abundant, but the cell processes were not very long and laid down only a minimal amount of intercellular collagen.

CASE 5.—M. S., a 70 year old woman, seen in January 1927, had had a slowly growing mass on the palmar aspect of the right forefinger for ten years. The presence of the mass caused considerable interference with manual work. Examination showed a hard, rounded, nontender swelling on the volar aspect of the distal phalanx.

Operation.—The mass shelled out easily, no attachments to nerves being seen.

Result.—The patient was not followed.

Pathologic Examination.—The encapsulated pearly gray mass measured 2 by 1.5 by 1 cm. Cross-sections showed no degenerative changes.

The microscopic picture was typical for a neurofibroma. It was of low cellularity, with abundant intercellular collagen and little evidence of degeneration.

CASE 6.—B. G., a 22 year old man, entered the hospital on Nov. 8, 1915, because of a painful tumor in the left buttock and a painful swelling of the forearm. For five years there had been pain and tenderness in the left hip, and for four years there had been occasional, increasingly severe pain radiating down the back of the leg. For seven months there had been a large lump in the left buttock. For one year he had also had a slowly growing and painful mass on the back of the left forearm. Examination showed a hard, rounded, tender, deeply attached swelling in the lower part of the left buttock (fig. 11), and the left gluteal fold was lower than the right. The left leg was slightly smaller than the right. Motions of the hip were somewhat limited because of pain. On the back of the left forearm, halfway between the elbow and the wrist, was a tender, deep swelling. The left hypothenar eminence was somewhat smaller than the right. Extension of the fingers was not quite complete at the first interphalangeal and metacarpophalangeal joints. The patient had none of the stigmas of Recklinghausen's disease. This case had unusual interest because of the presence of neurofibromas in two siblings, unassociated with Recklinghausen's disease (the patient in case 7 and one brother not treated by us). These three cases have been previously recorded by Fleming and Marvin.[23]

Operation.—Operation on the left thigh disclosed an encapsulated growth about the size and shape of a lemon which lay directly in the middle of the sciatic nerve, the fibers of which were spiraled around the growth. The nerve was split for a distance of 8 cm., and the tumor was easily shelled out in toto. The mass removed from the dorsal aspect of the left forearm arose from the posterior branch of the ulnar nerve, from which it was peeled away without severing the nerve.

Result.—There was complete relief from pain, without loss of sensory or motor function, in the arm and leg. There was no recurrence of either growth when the patient was last seen in 1927.

Pathologic Examination.—The tumor of the arm consisted of a firm, gray, semitranslucent, oblong, smooth, somewhat nodular but well encapsulated mass, measuring 4.5 cm. in length and 1.8 cm. in diameter (fig. 12*A*). The cut surface was smooth, moist and myxomatous.

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23. Fleming, L. N., and Marvin, F. W.: Familial Fibromyxomata of the Peripheral Nerves, Surg., Gynec. & Obst. **24**:287, 1917.

Microscopically, there was a relatively low cellularity to the tumor, the wavy connective tissue cells laying down abundant collagen and also showing a myxomatous type of growth. No mitotic figures were seen. Interlacing bands of fibers, with a suggestion of palisading of the nuclei, gave a characteristic picture of neurofibroma.

The tumor of the leg was oblong, smoothly encapsulated, slightly irregular and lemon shaped and weighed 122 Gm. (fig. 12 *B*). It was firm, gray and slightly elastic. The cut surface was smooth, myxomatous and practically colorless. A few areas of the cut surface had the appearance of faint, interlacing bundles of connective tissue.

Microscopically, there were interlacing strands of wavy connective tissue in a loose-textured type of growth which had the general appearance of a neuro-

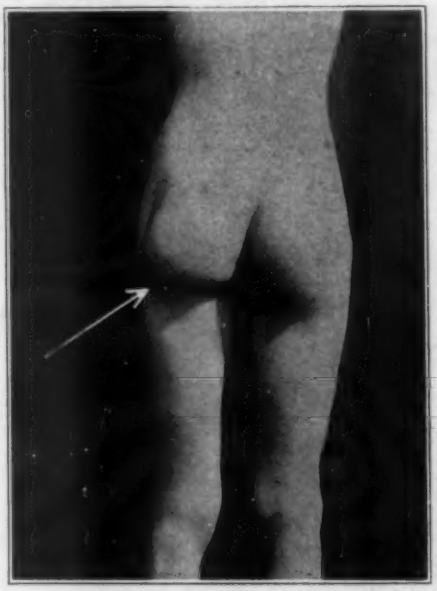

Fig. 11 (case 6).—Photograph of the patient to show swelling of the left buttock produced by a neurofibroma of the sciatic nerve.

fibroma. The nuclei and cytoplasms were elongated. Many of these cells were laying down considerable amounts of collagen. Edema and degenerative changes were marked. The mass had a well developed fibrous capsule.

Case 7.—A. S. (sister of B. G., case 6), a 32 year old woman, entered the hospital on Nov. 3, 1915, with the complaint of pain in the lumbar portion of her back, radiating down to the posterior part of the right leg, and weakness of her right leg for one year. (Fifteen years previously she had had a "fibroid tumor" the size of a small orange removed from the right side of her neck in another hospital.) She dated her present illness from a fall eighteen months prior to entry, at which time she sat down heavily and received a severe jar. On subsequent development of pain in the back and legs, she had been placed in a plaster jacket for spinal immobilization. Two months prior to the time when we first saw her she had been operated on elsewhere (for tumor of the spinal cord [?]).

and a dorsal laminectomy had been performed with negative results and with no relief from symptoms. Examination showed limitation of flexion of the right hip and foot because of pain which the movements excited. In the right subgluteal fold an indistinct deep mass was palpable. There were areas of anesthesia over the dorsal surface of the toes of the right foot, extending up a distance of 2 or 3 cm. onto the dorsum of the foot and also spreading over a strip on the lateral aspect of the foot as far as the ankle. There was also a questionable

Fig. 12 (case 6).—*A*, a neurofibroma removed from the dorsal aspect of the forearm. The specimen measured 4.5 cm. in length and 1.8 cm. in its maximum diameter. *B*, a neurofibroma removed from the left sciatic nerve. (See *A*.) The specimen was lemon sized, weighing 122 Gm.

area of anesthesia over the posterior aspect of the right calf along the distribution of the first and the second sacral nerve.

Operation.—The sciatic nerve was exposed and was found to contain a large bulbous swelling surrounded and enclosed by the fibers of the nerve. An incision was made through the nerve capsule, and it was somewhat difficult to tell just

which was the proper layer for enucleation. It was finally possible, however, to tilt the tumor up from below by blunt dissection and to follow it into the sciatic notch. In the final stages of delivery the mass was broken into in its upper pole, and undoubtedly some fragments were left in the operative field. The thin nerve capsule was now allowed to collapse, the procedure invoking but little damage to the nerve trunk.

Result.—Complete relief from pain was obtained, but there were residual areas of anesthesia on the sole of the foot and also surrounding the internal malleolus. Four months later there was return of pain in the foot, and there was an obvious recurrence of an infiltrating tumor deep in the buttocks. The patient died within a year of pulmonary metastases while at another hospital. Permission for autopsy was not obtained.

Pathologic Examination.—The pear-shaped, slightly yellowish, but rather translucent tumor measured 10 by 9 by 6 cm. A cross-section showed three large cystic cavities filled with vesiculated tissue. The remaining mass was opaque, white, myxomatous and necrotic.

Microscopically, the neoplasm was a very cellular, highly malignant fibrosarcoma. The closely packed nuclei were oblong, loose textured young forms. There was no palisading of nuclei. There was only slight formation of intercellular substance. Mitotic figures were numerous. Areas of degeneration and necrosis were extensive.

CASE 8.—P. T. C., a 42 year old man, was seen on April 25, 1916, complaining of a swelling on the lateral aspect of the left knee, a toe drop and pain in the knee and ankle for nine months. Examination showed a hard, tender swelling, about 2 cm. in circumference, superficial to and just below the head of the left fibula. Touching this mass caused a prickling sensation in the great toe and the second toe. There was inabilty to dorsaflex the great toe, and an area of hypesthesia was found over the great and the second toe which extended up for a distance of 3 cm. onto the dorsum of the foot.

Operation.—Operation disclosed a swelling in the peroneal nerve, the nerve trunk above and below this bulbous enlargement being entirely normal. The outer fibers of the nerve were split longitudinally, bringing into view a cyst 3 cm. in length, around which the central bundles of the peroneal nerve coursed (fig. 13). It was then possible to enucleate the cyst in its entirety, cutting across only a few nerve fibers at either end of the cyst. The split nerve was allowed to collapse and was dropped back into the wound.

Result.—After the operation limitation of motion of the foot and toe and the areas of anesthesia were practically the same as before operation. In about one year all sensory loss had been regained, and the muscular control of the left great toe and the left foot had returned to normal. The patient has been followed until 1935 and has had no recurrence of the mass on the lateral aspect of the knee.

Pathologic Examination.—The mass proved to be a cystic structure about 3 cm. in length and 1.5 cm. in diameter. There was a thin, grayish capsule, which was filled with a yellowish gelatinous substance but no solid tumor tissue.

Microscopically, the wall of the cyst was composed of a thin, fibrous structure in which the individual cells were elongated and very narrow and had slightly wavy cell nuclei and cell fibrillae. These spindly cells had a slight tendency to occur in interlacing bands, but there was no evidence of palisading of nuclei. There was a small amount of intercellular collagenous substance. There were no mitotic figures. There was obvious cystic degeneration in this thin bit of

remaining tissue, and the central gelatinous substance was mucoid in appearance and took a deep basophilic stain. Along the outer aspect of the fibrous capsule there were a few medullated nerve fibers. Knowing the tendency of a neurofibroma to break down and become cystic and having the small bits of tissue histologically remaining in the wall of this cyst which are consistent with neurofibroma, we are forced to the conclusion that this myxomatous cyst of the peroneal nerve had its origin in a previously existing neurofibroma.

CASE 9.—T. M., a 48 year old man, was seen in December 1923 for treatment of a slowly growing, nonpainful mass over the right ankle, which he had had "all his life." Examination showed an elastic, tense, bilobed, partially fluctuant and partly solid tumor 15.5 cm. long, 7 cm. wide and 5 cm. in thickness over the right external malleolus.

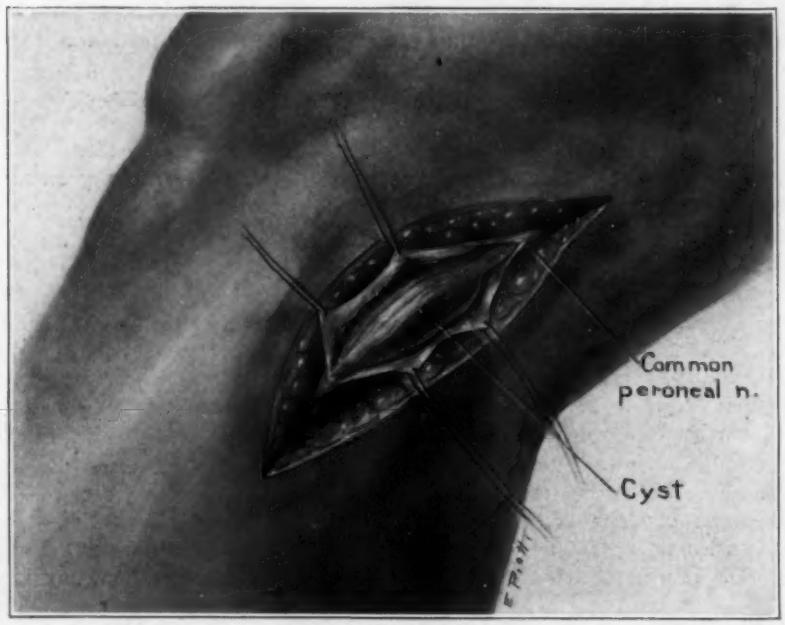

Fig. 13 (case 8).—A cyst in the substance of the common peroneal nerve, originating in a degenerated neurofibroma. The outer portion of the nerve has been incised longitudinally, and the cut edges are retracted with silk threads. The cyst lying in the central portion of the nerve trunk is surrounded by some nerve fibers from the central part of the trunk. Only these central fibers (seen at either end of the cyst) were divided in removing the cyst.

Operation.—On operation the tumor was found to extend deeply between the tendons. It was closely adherent to the periosteum of the fibula and was attached to the superficial peroneal nerve, from which it was peeled away.

Result.—There had been no recurrence up to 1932, at which time the patient was lost from observation.

Pathologic Examination.—The ovoid tumor measured 15.5 by 7 by 5 cm. The major portion of the well encapsulated mass was necrotic and cystic, and incision

allowed the escape of 200 cc. of thin, rather bright red bloody liquid. The cavity was one with ragged recesses and irregular projections of gelatinous yellowish tissue, having about the consistency of fibrinous exudate. About one third of the cyst was lined by translucent, yellowish gelatinous material, alternating with a dark red firmer substance. Incision of various portions of the tumor revealed calcified material in the capsule.

Microscopically, the better preserved portions of the tumor showed irregular interlacing small bundles of elongated cells in arrangements typical of a neurofibroma. No mitotic figures were seen. The nuclei varied a little more in size and shape than is usually seen in the average neurofibroma. The long cytoplasmic processes were laying down a fairly abundant intercellular collagenous material. The tumor varied considerably in cellularity from place to place. There were marked degenerative changes.

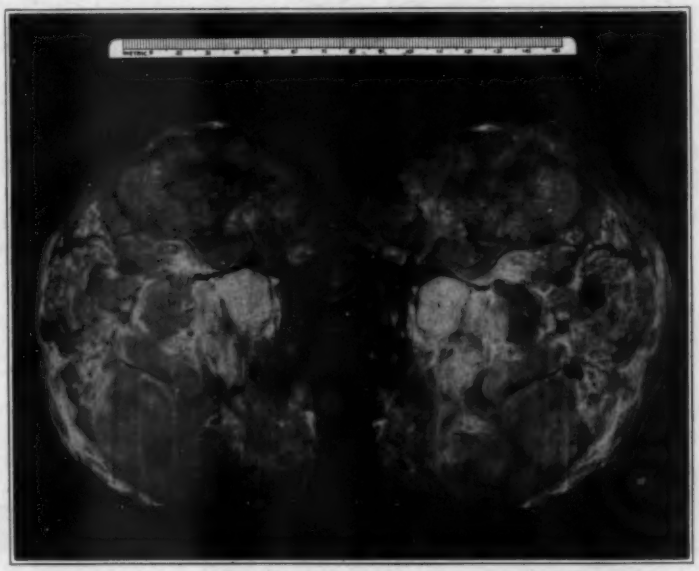

Fig. 14 (case 10).—Photograph of a large fibrosarcoma (which arose from the sciatic nerve and infiltrated the overlying hamstring muscles).

Case 10.—E. P., a 74 year old man, entered the hospital on May 23, 1934, because of a swelling in the right thigh and pain in the right leg for nine months. Examination showed a large, firm, rather elongated, slightly tender mass about the size of a large grapefruit in the upper third of the posterior aspect of the right thigh. Roentgen examination showed a soft tissue swelling in the thigh and definite destruction of the tuberosity of the right ischium indicating invasion by tumor.

Operation.—On operation the large mass was found to be intimately adherent to the overlying muscle bundles (fig. 14). It was impossible to uncover the sciatic nerve at the upper end of the wound, though it was exposed at the lower pole of the tumor as it emerged from the tumor mass. The tumor was split, and the major strands of the sciatic nerve were pulled aside. The neoplasm was then

shelled out and was separated as well as possible from the surrounding soft muscular tissues. Complete extirpation of this obviously malignant tumor was impossible, and since the patient had refused amputation an attempt was made to remove only the greatest bulk of the growth in order to relieve the local discomfort.

Result.—Local and regional roentgen irradiation was given in four courses of treatment during the following seven months, at the end of which time pulmonary metastases were evident in roentgenograms. The patient died one year after operation, obviously with extensive pulmonary metastases. Permission for autopsy was not obtained.

Pathologic Examination.—The partially encapsulated, irregular and torn tumor weighed 827 Gm. and measured 18 by 12 by 10 cm. One side showed large amounts of myxomatous material, which were intermingled with zones of white,

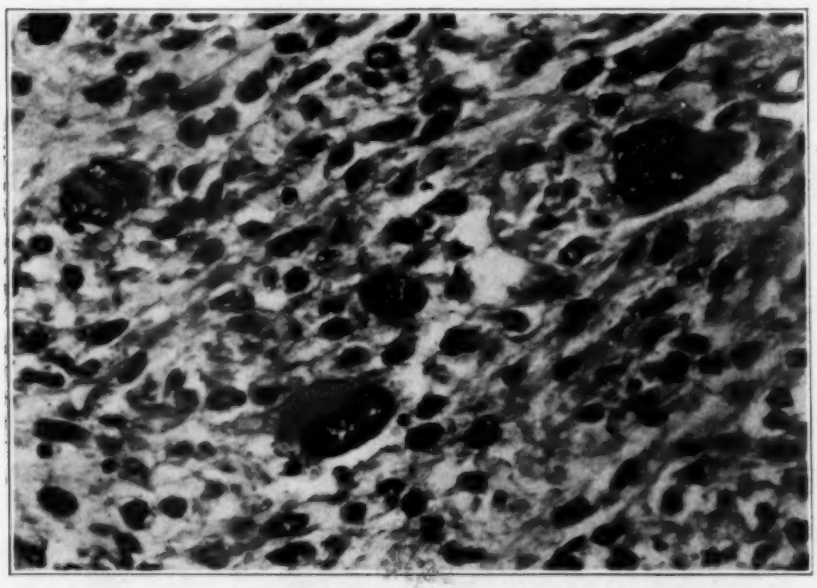

Fig. 15 (case 10).—Photomicrograph (× 370) of a rapidly growing fibrosarcoma originating from the sheath of the sciatic nerve. The nuclei present great variation in size. Multinucleated cells are common. (Other fields contained many mitoses.)

firm, fibrous substance. At the lower end of the tumor some fragments of the nerve trunk were seen to blend with the tumor and become inseparable from it. Cut section showed a yellowish gray appearance, varying from myxomatous material to soft and necrotic or to firm and better preserved tissue.

The histologic picture was that of a rapidly growing sarcoma, the microscopic as well as the gross structure being characterized by great variability. The highly cellular growth showed a great range in size, shape and staining properties of nuclei (fig. 15). Multinucleated cells were common, and mitoses were numerous. Collagen was seen in small amounts, and extensive areas of necrosis and hemorrhage were common.

CASE 11.—L. A., a 40 year old woman, was seen on Sept. 6, 1935, complaining of a small area of tenderness just below the right internal malleolus for three years. Examination disclosed a distinct swelling about 1 cm. in diameter.

Operation.—The well encapsulated mass was easily peeled away from the posterior tibial nerve.

Result.—There were no areas of anesthesia or motor disturbance in the foot after operation.

Pathologic Examination.—The firm, pinkish gray, encapsulated nodule measured 1 by 0.9 by 0.6 cm. The cut surface was firm and gray, but scattered through it were small brownish areas.

The histologic picture was one of a typical, slowly growing neurofibroma, showing small zones of early necrosis and deposition of blood pigment.

CASE 12.—F. H., a 19 year old youth, was seen on March 16, 1917, complaining of a nontender but gradually increasing swelling in the left side of the neck of three years' duration. Posterior to the upper insertion of the sternocleidomastoid muscle was a rounded, immovable, firm mass 6 cm. in diameter. Roentgen examination of the neck showed an area of rarefaction in the left side of the bodies of the fourth and fifth cervical vertebrae, suggesting pressure atrophy.

Operation.—An encapsulated mass was found to be in contact posteriorly with the erector spinae and longus colli groups of muscles and above lay along the lower surface of the skull. This was gradually freed by blunt dissection. The tumor appeared to have no pedicle or point of attachment. It was not known from which nerve the mass arose.

Result.—The patient was not followed.

Pathologic Examination.—The mass was smoothly rounded and well encapsulated and measured 4.5 cm. in diameter. The central part of the tumor was necrotic, gelatinous and translucent and had intermingled areas of hemorrhage. The peripheral portions of the tumor showed some solid white fibrous tissue from 2 to 5 mm. in thickness where the neoplasm was better preserved.

Microscopically, all of the sections showed typical neurofibroma and the histologic details of this type of growth. There were, however, widespread edema, evidence of degeneration with loss of histologic structure, infiltration with large phagocytes and the formation of cystic spaces ranging from 1 to 3 mm. or more in diameter.

CASE 13.—P. H., a 69 year old man, was seen on Nov. 19, 1919, with a chief complaint of cervical discomfort and a gradually increasing swelling of the left side of the neck for four months. Associated with this there had been moderate pain radiating up the left side of the neck and the region of the mastoid. During this time there had been slight hoarseness. Examination showed a pulsating, nontender swelling 2 cm. in diameter just above the bifurcation of the carotid artery. The left pupil was smaller than the right, but both reacted to light and in accommodation.

Operation.—On operation the lower portion of the internal carotid artery was found to be greatly twisted and looped on itself, but no other mass was discovered during cervical exploration. (Very likely there was a small mass deep to this convoluted vessel which was missed during the operative exposure.)

Second Entry.—The patient was not seen again until 1924, when he returned to the hospital because of progressive enlargement of the cervical mass. During the six year period there had been only moderate discomfort until five months

before entry, when the swelling became distinctly painful, with radiation from the angle of the jaw to the region of the left mastoid and occipital area as well as to the temporal region and the lateral aspect of the left eye. There was a mild unproductive cough. On the left side of the neck, slightly below the angle of the jaw, there was a firm, nontender, irregular mass 4 by 5 cm. in length and breadth. The left pupil was of pinpoint size and reacted sluggishly to light.

Operation (Jan. 11, 1924).—Operation revealed a rounded tumor beneath the sternocleidomastoid muscle, which had its origin high in the neck. The common carotid artery had been pushed inward and anteriorly. The mass was excised, being freed from the base of the skull where it was attached to a nerve which was obviously the vagus. This nerve was completely severed, no nerve suture being possible because of the gap produced in the nerve trunk.

Result.—The voice remained permanently husky (loss of function of the recurrent laryngeal nerve). There was complete relief from pain. There had been

Fig. 16 (case 13).—Neurofibroma removed from cervical portion of the vagus nerve.

no recurrence of pain or of the mass up until 1929, when the patient died of pneumonia. (This case has particular interest from the consideration of complete division of the left vagus nerve, for during the five years of life after division of this nerve we were unable to detect any change in the cardiac mechanism or variation in function of the abdominal viscera.)

Pathologic Examination.—The oval, irregular, lobulated, gray and pinkish, encapsulated mass measured 6 by 4 by 3 cm. and weighed 32 Gm. (fig. 16). Some areas were firm and others were somewhat soft. The cut surface was homogeneous, but in the opaque white substance were small hemorrhagic areas.

Microscopically, there was a low cellularity, an interlacing of bundles of spindle-shaped cells, with long, delicate cytoplasmic extensions and some deposition of intercellular collagen. The cells had oval, slightly granular nuclei with scanty cytoplasm, the nuclei being frequently arranged in definite palisades, and in some areas this finding was striking. No mitotic figures were encountered. A few scattered areas showed some evidence of early degeneration.

Case 14.—C. H., a 38 year old man, was first seen on Sept. 26, 1930, because of swelling on the left side of the neck which had been progressively increasing in size for fifteen years. Operation on this mass had been performed at another hospital one year previously, and a large cyst was entered which was said to be "the size of a grapefruit." It was firmly adherent to the surrounding structures, and attempts at excision were not made. Examination now revealed a conspicuous ovoid, rather smooth, semifluctuant mass, approximately the size of two fists, which extended from the angle of the jaw down nearly to the clavicle. It could be moved quite freely from side to side but not up and down. Involvement of the recurrent laryngeal nerve was suggested by the presence of hoarseness.

Operation.—The tumor was outlined posteriorly, inferiorly and medially. The carotid artery was finally exposed as it lay on the medial aspect of the tumor,

Fig. 17 (case 14).—Cut surface of a large cervical neurofibroma arising from the vagus nerve.

together with a large nerve, which was proved to be the vagus. Without great difficulty a complete enucleation of this tumor was effected (without severing the nerve). Posteriorly, the mass lay against the transverse processes of the cervical vertebrae, passing upward nearly to the base of the skull.

Result.—The patient has been followed until April 1935, with complete relief from symptoms and without evidence of recurrence.

Pathologic Examination.—The tumor was roughly elliptical, smooth and well encapsulated; it weighed 253 Gm., and measured 10.5 by 7 by 6 cm. The cut surface presented a solid, glistening, yellowish gray tissue, with small punctate areas showing necrosis (fig. 17).

Microscopically, the better preserved areas showed anastomosing bands of elongated and narrow, fusiform cells, with long wavy fibrillae, showing charac-

teristic structures of a neurofibroma. There was some palisading of nuclei. There was evidence of extensive degeneration as shown by edema of the tumor and presence of numerous vacuolated foam cells.

Case 15.—A. C., a 70 year old woman, was seen on Sept. 11, 1931, complaining of a mass on the left side of her neck which had gradually increased in size over a period of ten years. At the angle of the jaw was a firm, nontender,

Fig. 18 (case 15).—*A*, external surfaces of a well encapsulated cervical neurofibroma. *B*, cut surfaces of a cervical neurofibroma, showing extensive central degeneration and cyst formation.

slightly movable, questionably cystic swelling about the size of a lemon, extending from the lobe of the left ear to about 4 cm. above the clavicle.

Operation.—On operation a large tightly stretched nerve was found coursing transversely across the upper portion of the tumor. There was a similar nerve

trunk stretched transversely across the lower pole of the mass. It was impossible to identify with certainty these nerve structures. It was certain, however, that they were not the spinal accessory nerves or portions of the ansa hypoglossi nerves. These were dissected upward and downward, and the tumor was then freed from the surrounding tissue without breaking its capsule.

Result.—The patient was last seen in January 1935, at which time there was no evidence of recurrence.

Pathologic Examination.—The well encapsulated, ovoid tumor measured 8 by 5 by 4.5 cm. and weighed 75 Gm. (fig. 18*A*). Cut section showed a cystic and necrotic center with better preserved tumor tissue at the periphery (fig. 18*B*).

Fig. 19 (case 15).—Photomicrograph (× 170) of a benign neurofibroma with typical palisading of nuclei.

Microscopically, the cells were elongated and spindle shaped, but wavy, with long fibrillar structures, between which there was an abundance of intercellular collagen. Nuclei were elongated and slightly wavy. There was a marked tendency to palisading of nuclei (fig. 19). In many areas there was evidence of degeneration and cyst formation. The picture was typical of a degenerating neurofibroma.

Case 16.—L. B., a 66 year old woman, entered the hospital on Feb. 1, 1935, complaining of a mass on the left side of the neck which had been present for three years. While growth had been slow at first, the mass had rapidly increased in size during the last year. There was a marked swelling of the left side of the neck, extending from the angle of the jaw down to a point about opposite the level of the hyoid bone. Palpation revealed a firm, freely movable, somewhat cystic-feeling mass, which was nontender. At first, it seemed as if it

pushed the carotid vessels forward, a pulsation being prominent on the anterior aspect of the mass. The swelling was about 7 cm. in length, the long axis being in the vertical plane of the body, and about 3.5 cm. in width. There was edema of the left tonsil and a marked bulge in the left tonsillar fossa.

Operation.—Operation disclosed the tumor partly overlain by the internal jugular vein and its branches, and it was necessary to tie these off and resect them from the lower part of the tumor. The external carotid artery had been pushed forward by the mass, and the internal carotid artery was greatly displaced

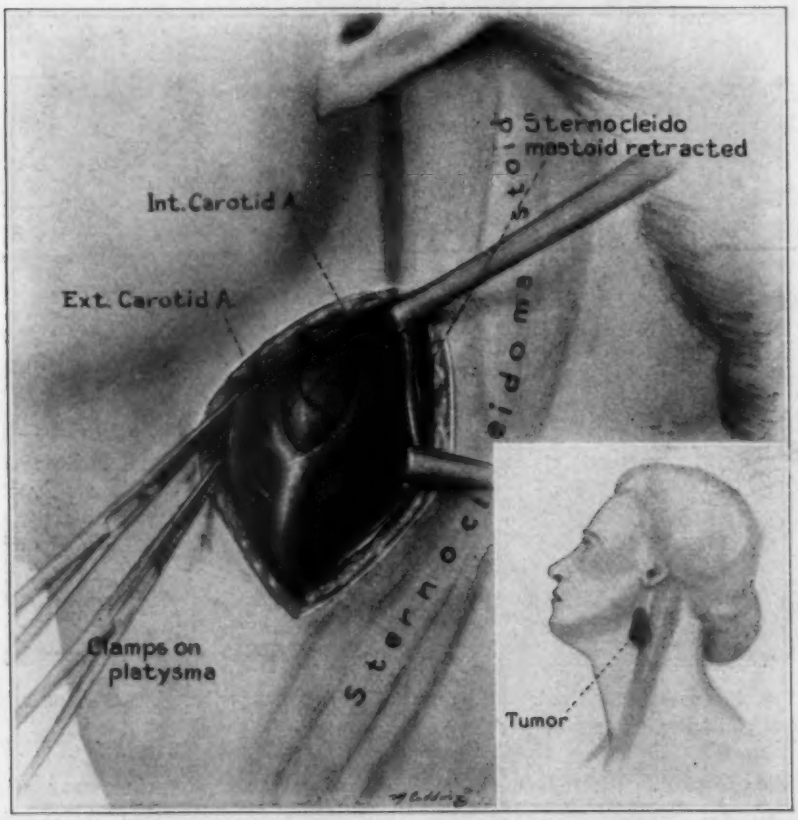

Fig. 20 (case 16).—Drawing of the operative field, with the tumor (cystic neurofibroma) lying deep in the cervical tissues and bulging the external carotid artery forward and the internal carotid artery laterally. The superior laryngeal nerve loops across the lower pole of the mass. A segment of the internal jugular vein has been resected to gain access to the tumor. (From *Ann. Surg.* **104**:436 [Sept.] 1936).

laterally (fig. 20). A nerve, which seemed to be the vagus, was dissected off the mass laterally, and the superior laryngeal nerve, which had been pushed down the neck a long distance, was dissected off inferiorly. Eventually, by careful dissection, the upper pole was detached from the anterolateral surface of the

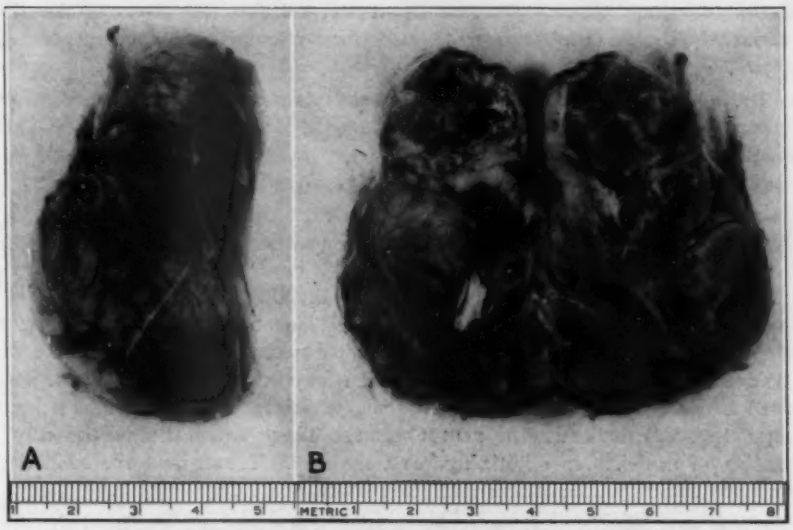

Fig. 21 (case 16).—*A*, external view of a cervical neurofibroma. *B*, cut surface of the cervical neurofibroma with extensive cystic degeneration. The specimen consists of little more than a shell, traversed by remaining trabeculae.

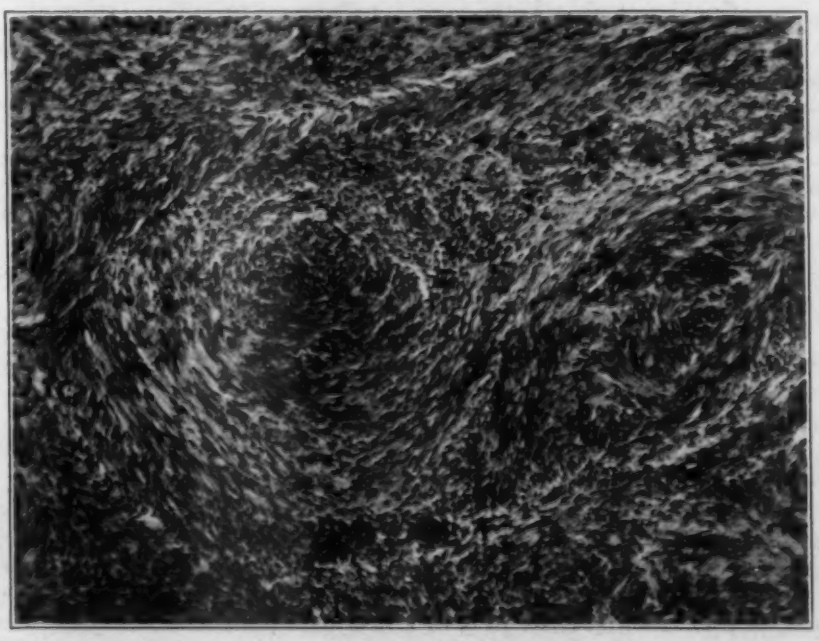

Fig. 22 (case 16).—Photomicrograph (× 140) from a small remaining portion of solid tissue (fig. 21 *B*) of a cystic cervical neurofibroma. Cells of mature type are seen in greatly interlacing bundles and whorls.

vertebral column, high up past the tonsil and close to the floor of the skull. (Presumably the mass arose from the anterior root of one of the upper cervical nerves.)

Result.—No paralysis or sensory loss could be detected after operation. There has been complete relief from symptoms, and up to the present time (October 1935) there is no evidence of recurrence.

Pathologic Examination.—The cystic mass removed was 6 cm. long, 3.5 cm. wide and 2.5 cm. thick. There was a continuous, tough, gray capsule (fig. 21*A*). When sectioned, in the greater portion of the specimen was a multilocular structure surrounded by a thin, fibrous wall about 1 mm. in thickness and traversed by fine, thin trabeculae and fibrous septums, dividing it into thin-walled cysts containing a clear, watery fluid. Toward one side of the specimen was a mass of dense gray to grayish white, rather firm substance, as shown in figure 21*B*.

Microscopically, the capsule as well as various portions of the trabecular tissue showed a dense fibrous structure with some whorl formation and interlacing of bundles (fig. 22) indicative of neurofibroma. There was little in the way of palisading of nuclei. No mitotic figures were seen. Throughout the solid tissue there were small cystlike spaces and other evidence of degeneration.

Case 17.—A. R. S., a 36 year old woman, was seen on Nov. 30, 1922, complaining of a small nontender, slowly growing mass in the left side of the neck for eight years. At times when she moved her left arm there was a slight tingling sensation in the region of the left elbow. In the left side of the neck, just above the outer end of the clavicle, was a hard mass about 2.5 cm. in diameter, located beneath the skin and in the subcutaneous tissues. It was freely movable and could be pushed down under the clavicle.

Operation.—Dissection was carried down to the lateral trunk of the brachial plexus, from which the tumor arose. The mass was attached to the trunk between the origin of the suprascapular and that of the musculocutaneous nerve. The fibers of the lateral cord on reaching the tumor spread out diffusely over it, but the major number were grouped fairly definitely in a wide bundle along its under-surface. Enucleation was performed, leaving a rather broad band of fibers connecting the normal distal and the proximal portion of the nerve, which, as stated, went over the inferior aspect of the tumor.

Result.—After operation there was no area of anesthesia of the arm, and there was no evidence of any muscular weakness. The patient was not followed.

Pathologic Examination.—The specimen was irregularly shaped, smooth, pinkish gray and glistening and measured 2.5 cm. in diameter. On section there was a variegated appearance, some areas being rather firm, grayish white and glistening, while others were yellowish gray, soft and partially necrotic.

The microscopic picture was typical of a neurofibroma with many areas of degeneration and small cavity formation.

Case 18.—M. G., a 23 year old man, was seen on May 31, 1933, complaining of a lump in the left side of the neck of four months' duration. For one year there had been frequent attacks of sharp pain in the dorsum of the left hand, over the region of the first metacarpal bone. He found that each attack of pain had been preceded by pressure of some sort in the left supraclavicular area. In the left supraclavicular region was a firm swelling about 5 cm. in diameter, which could be felt below as well as above the clavicle.

Operation.—Operation disclosed that the mass originated in the posterior cord of the brachial plexus (fig. 23). The tumor was completely excised along with

a segment of the cord from which it arose. The fragments of the posterior cord which had been severed were now reapproximated with silk sutures. The arm was immobilized in an airplane splint.

Result.—After operation the patient had, of course, complete paralysis of the radial and axillary nerves. In eight months the wrist drop was still complete, but in fourteen months there was fairly good dorsiflexion of the hand, and he suffered no real disability. In October 1934, seventeen months after operation, the patient had complete use of the arm and full power of every muscle. The area of anesthesia in the arm gradually disappeared, so that at the end of two years there was complete return of sensory function. At the present time, October 1935, there is no evidence of recurrence of the growth.

Pathologic Examination.—The well encapsulated, soft, oval tumor measured 4.7 cm. in length and 2.4 cm. in diameter. Branches of the posterior cord ran along in the capsule. The cut surface was light beige and had a slightly translucent, succulent and plexiform appearance, some areas showing mild cystic degeneration.

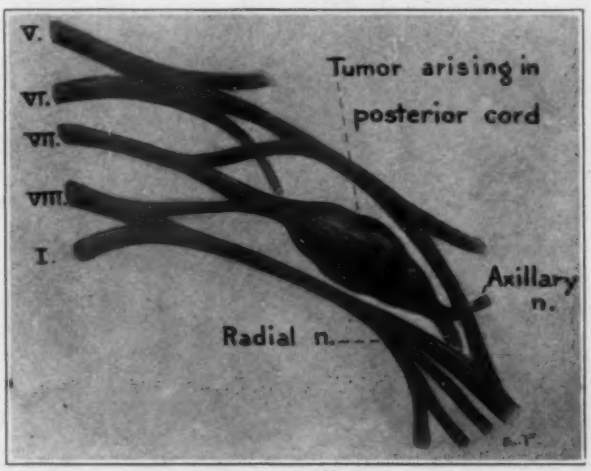

Fig. 23 (case 18).—Schematic drawing of the left brachial plexus to indicate the position of a malignant neurofibroma arising in the posterior cord. In this case the entire tumor and a segment of posterior cord were excised, followed by an end to end suture of the severed parts of the posterior cord. (Complete function of axillary and radial nerves subsequently restored.)

Microscopic examination showed a higher cellularity than that found in an ordinary neurofibroma. While many of the cells were of mature type and the nuclei were elongated and spindle shaped, there were other areas in which the nuclei were of a distinctly younger form. These were oval, at times almost rounded, having only a light chromatin network which was well dispersed (fig. 24). Many of the cells contained one or two small nucleoli. Mitotic figures were occasionally encountered. There was a rare suggestion of palisading of the nuclei. The cells often showed interlacing bundles and whorl formation. The relatively high cellularity of the tumor, the somewhat immature appearance of the cells and the presence of mitotic figures marked this neoplasm as having a distinctly

higher malignancy than the average neurofibroma. The changes, however, were not sufficient to make a diagnosis of neurofibrosarcoma, and we have listed it as a malignant neurofibroma to indicate the rate of growth. The microscopic picture justifies the complete removal of the mass with its nerve trunk, for dissecting such a growth from its nerve would certainly have led to recurrence.

CASE 19.—J. M. P., a 32 year old woman, entered the hospital on June 6, 1933, the chief complaint being intermittent pain in the left temporal and malar regions of the face of seven years' duration, and swelling in the left subtemporal region for two months. There was a continuation of the mass internally, for the left side of the pharyngeal vault protruded much more than the right. External aspiration produced 15 cc. of serohemorrhagic fluid. Sodium iodide was injected into this cavity, and roentgenograms (fig. 25) showed an irregular cyst from

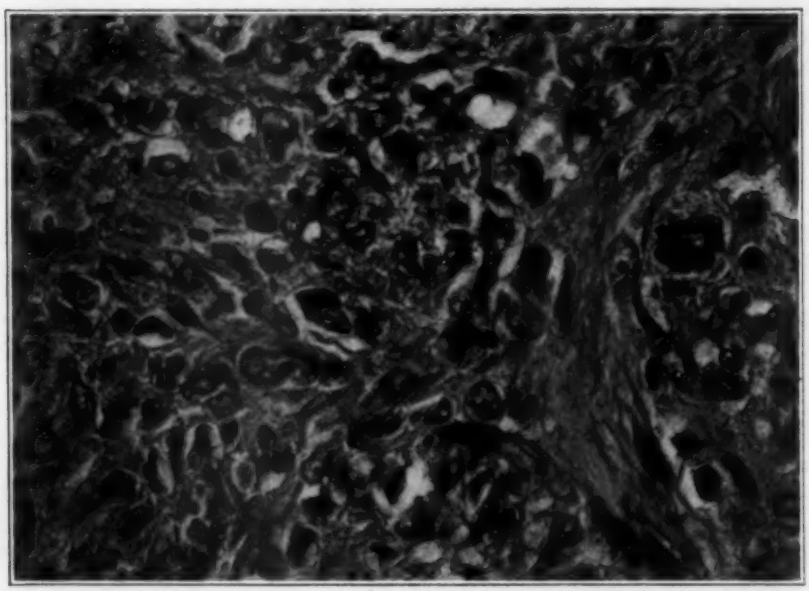

Fig. 24 (case 18).—Photomicrograph (×660) of a malignant neurofibroma of the brachial plexus. There are fairly abundant cytoplasmic fibrillary processes and intercellular collagen. The nuclei have considerable variation in size and shape. One mitotic figure is seen toward the right.

3 to 5 cm. in principal diameters, lying largely in the lower portion of the temporal fossa, but also extending through the pterygopalatine fossa down into the soft palate. There was, in addition, intracranial extension through the great wing of the sphenoid bone, for the lateral and the posterior wall of the orbit were eroded.

Operation (June 9).—An incision was made over the mass externally, just above the left zygoma. The wound was deepened until a tough wall was encountered. A fragment of the wall of the cyst was removed for microscopic examination. The opened cyst was then thoroughly treated with sclerosing fluid, and the wound was packed open to allow for drainage. At the time of discharge from

the hospital on the fifth postoperative day, the pack had been withdrawn and the wound was beginning to heal.

Pathologic Examination.—The material removed from the wall of the cyst showed fibrous tissue with no evidence of neoplasm.

Second Entry.—The patient again entered the hospital on July 19, with the complaint of intermittent pain in the left malar and left temporal region. Since the previous admission there had been recurrence of swelling in the left malar, left temporal and left pharyngeal regions. There was a marked swelling extending well into the soft palate, which, on palpation, was fluctuant and cystic.

Second Operation (July 20).—The cystic portion of the mass in the soft palate was incised, and the heavy sac of the wall of the cyst was exposed. An attempt was made to free the lower portion of the cyst, but it seemed so firmly adherent to the surrounding structures that attempts at removal were abandoned. A portion of the wall of the cyst was then removed for further histologic study.

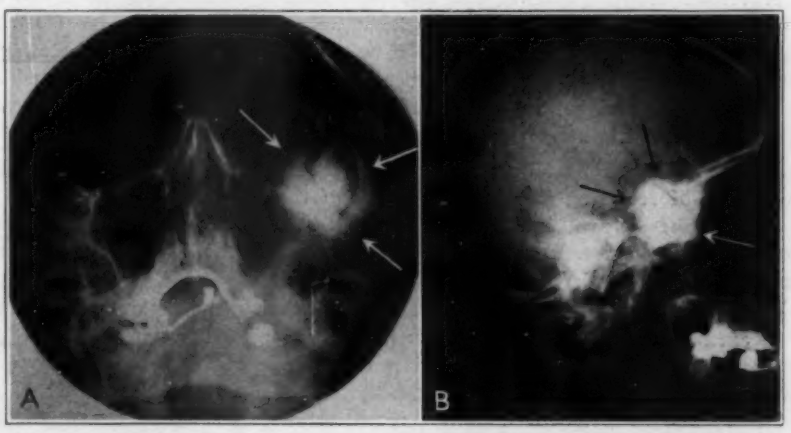

Fig. 25 (case 19).—*A*, postero-anterior view of the skull, showing a cystic neurofibroma of the temporal fossa (outlined by arrows) after the injection of sodium iodide. *B*, lateral view of the skull, indicating the position of the cystic neurofibroma of the temporal fossa (outlined by arrows) after the injection with sodium iodide.

A pack was placed in the palatine wound to allow for drainage, which subsequently continued for several weeks.

Pathologic Examination.—This portion of the wall of the cyst showed a fairly dense fibrous tissue with marked chronic inflammatory reaction. There was no evidence of neoplasm.

Third Entry (March 1934).—The patient had an infection of the upper respiratory tract, and subsequent to this there was a return and great increase in size of the swelling of the left side of the face. In addition, there was a mild exophthalmos on the left. The inside of the mouth showed a swelling on the left side of the roof, which was more pronounced than at any previous examination.

Third Operation (March 23).—An incision was made in the soft palate overlying the bulging cyst. A large fragment of the wall of the cyst was removed for microscopic study. Fluid in the cyst was purulent. The inner wall of the

cyst was then rapidly and thoroughly cauterized with sclerosing fluid. When the entire lining of the cyst, so far as could be visualized, was thoroughly charred, the cavity was wiped out with salt solution, and the wound in the soft palate was left open.

Pathologic Examination.—The material showed chronic inflammatory tissue among which were well preserved pieces of neurofibroma. (This presumably arose from the middle branch of the trigeminal nerve as it passes through the inferior orbital fissure. Such an origin would explain the orbital as well as the facial and palatine swellings.) One mitotic figure was found. Because of this, it was felt that this neurofibroma was more rapid in growth than the usual one, and hence the diagnosis of malignant neurofibroma was made. Because of this finding the patient was given roentgen irradiation over the left side of the face.

Result.—During the course of the next six months there was diffuse drainage of purulent material from the pharyngeal wound. This inflammatory process, however, appeared to have a beneficial effect in destroying the neoplastic growth, for by November 1934 all swelling had disappeared, exophthalmos was gone and the pharyngeal wound was healed. The patient up until the present time (October 1935) is free from symptoms and in marvelously improved health. However, check-up roentgenograms indicate further invasion of the orbital bones, and we are forced to believe that surgical intervention or roentgen irradiation may eventually be without avail.

Case 20.—J. H. P., a 35 year old man, entered the hospital on March 4, 1918, complaining of recurring pain in the left side of the chest for ten years. Just to the left of the sternum in the second and the third interspace was a distinct, rounded, slight protuberance, not quite as large as an area of dulness which lay under this and to the left of this region.

Roentgenograms showed a smoothly rounded shadow to the left of the ascending aorta, extending out about 2 cm. between the level of the first and that of the third rib. Fluoroscopy did not reveal any expansile pulsation, but there were movements of the mass synchronous with those of the aortic arch, against which it rested. The mass appeared to be in contrast with the anterior wall of the chest. It appeared to be about half under the sternum, reaching to the midline of the body, while the lateral half was out under the adjacent ribs and costal interspaces.

Operation.—With the patient under ether anesthesia, administered with a Connell apparatus, and in a supine position with the head slightly higher than the feet, a quadrilateral incision was made in the wall of the chest and carried down through the sternum and the second and the third ribs and cartilages on either side, making it possible to turn to the right a generous muscle and bone flap, opening into the superior mediastinum as by a trap door (fig. 26). An oval tumor mass at once presented, occupying the inner side of the sternum from the second and the third cartilage, extending upward to the first and downward to the fourth cartilage. A small amount of delicate overlying fascia was carefully dissected away, and as the right cleavage plane was reached it was now easily possible to enucleate an oval, slightly flattened tumor the size of a hen's egg. The chief attachments, which, however, were slender, were to the pericardium and the aorta on the one hand and the parietal pleura on the other. No definite nerve trunks were identified, but the mass probably arose from the phrenic nerve. The pleura had been pushed to the left by the growth of the tumor and offered no special difficulty. The osteoplastic flap was replaced and secured by two silver wires

passed through drill holes in the bone above and below. The second and third left costal cartilages were approximated with chromic catgut sutures. The soft tissues, anterior to the bony cage, were then brought accurately together.

Result.—The patient has been followed over a period of seventeen years until 1935. During this time he has been perfectly well, in excellent health, has had no recurrence of his preoperative symptoms and has been actively employed as an automobile mechanic. There have been no signs or symptoms of recurrence of the neoplasm.

Pathologic Examination.—The specimen was a flat, spheroid, smoothly encapsulated, yellowish, translucent mass, measuring 6 cm. in length, 5.5 cm. in width and 4 cm. in thickness (fig. 27 *A*). On section, the peripheral portions were

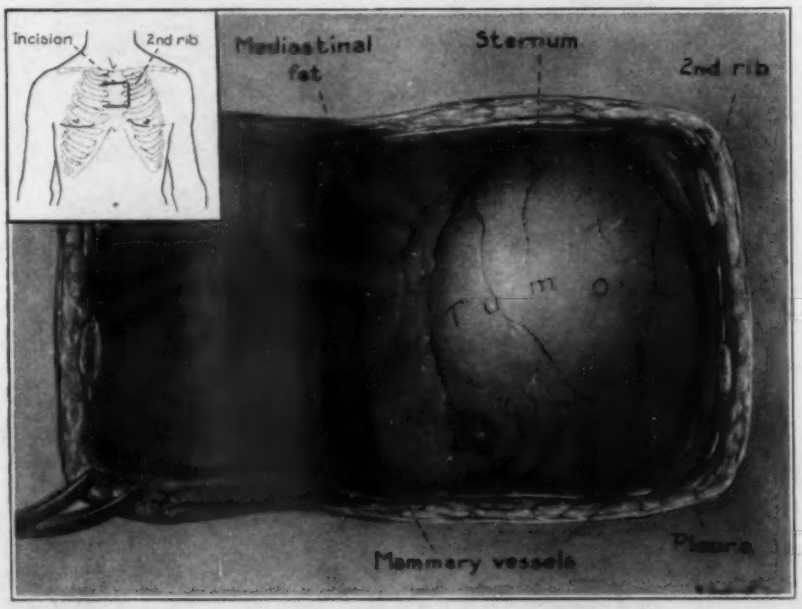

Fig. 26 (case 20).—Drawing of the operative field in exposure of a mediastinal neurofibroma. A trap door has been made in the anterior wall of the chest and is reflected toward the patient's right. The tumor was easily enucleated from its bed between the left parietal pleura and the great vessels of the superior mediastinum. The insert indicates the position of the surgical incision which was carried down through the sternum as well as the second and third costo-chondral cartilages on each side. (From *Ann. Surg.* **104**:436 [Sept.] 1936.)

translucent, edematous and moist, the bulk of the tumor consisting of necrotic, dark red, hemorrhagic material. There were several cysts filled with dark, bloody fluid (fig. 27 *B*).

Microscopically there were many different appearances in the various sections made from this tumor, largely explainable on the basis of degeneration and necrosis in a neurofibroma. The tumor, on the whole, was composed of mature spindle-shaped cells having a fine fibrillary intercellular collagenous substance (fig. 28). These cells in a few places had a whorl-like arrangement, with occa-

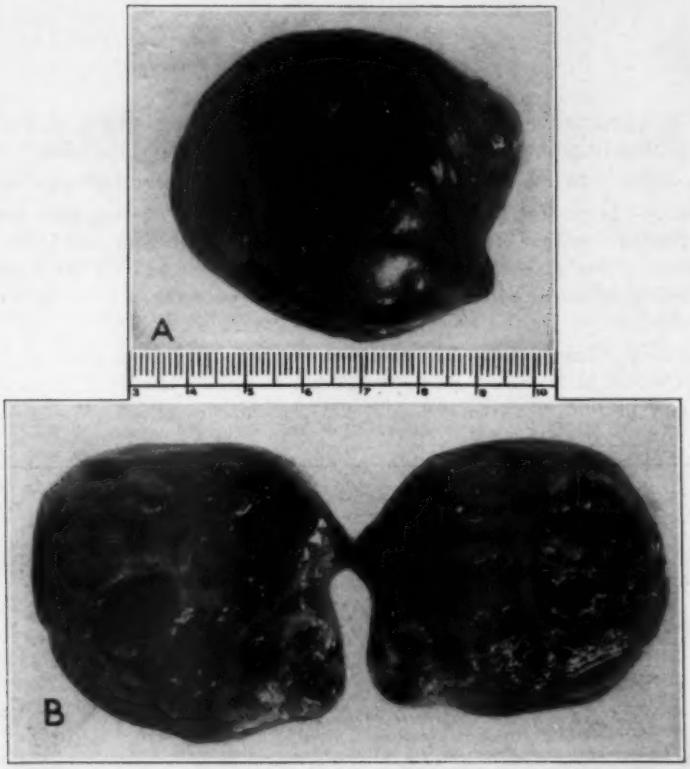

Fig. 27 (case 20).—*A*, external surface of a mediastinal neurofibroma. (Compare with figure 26.) *B*, cut surface of the neurofibroma, with multiple areas of hemorrhage and degeneration.

Fig. 28 (case 20).—Photomicrograph (× 100) of a mediastinal neurofibroma, with multiple areas of microcystic degeneration, many of which are filled with foamy, lipoid-laden phagocytes. The ruled-off zone at the top indicates the region shown in figure 29.

sional palisading of nuclei. There were prominent collections of large mononuclear cells with foamy cytoplasm, which stains for fat proved to be filled with lipoid droplets (fig. 29).

CASE 21.—S. S., a 27 year old woman, entered the hospital on Sept. 12, 1932, complaining of recurrent attacks of severe, sharp pain in the right side of the chest for five years. Examination showed an area of flatness to percussion, posteriorly on the right, from the seventh rib down to the base of the lung, extending from the spine out to the posterior axillary line. In this region the breath sounds were barely perceptible. Roentgen examination (fig. 30) disclosed a tumor about 10 cm. in diameter in the right side of the chest, posteriorly, which was apparently

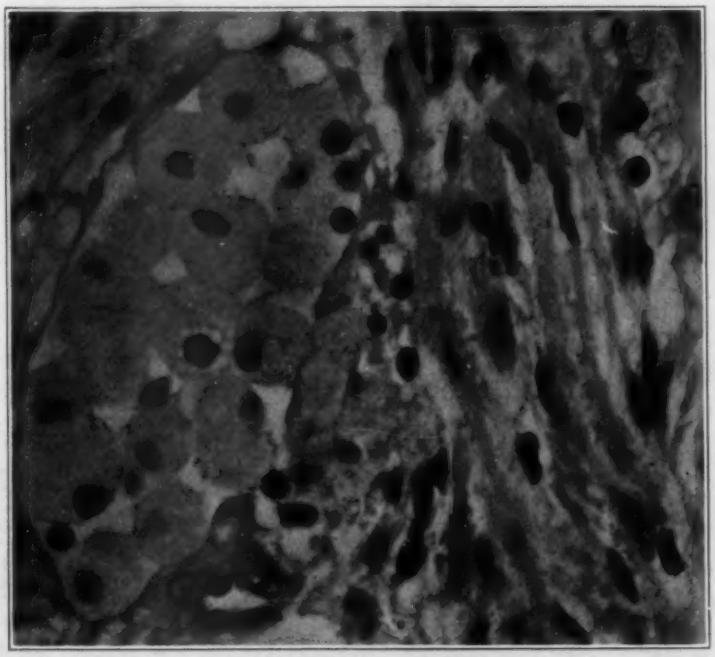

Fig. 29 (case 20).—Photomicrograph (× 600) of a mediastinal neurofibroma, with an area of cystic degeneration toward the left. This cyst is filled with large fat-laden phagocytes. (Compare with figure 28.)

separated from the heart, diaphragm and ribs. Fluoroscopy showed the mass to be adherent to the wall of the chest close to the spine. There was a definite thinning of the necks of the eighth and ninth ribs, close to the spine (pressure atrophy).

Operation.—Ether anesthesia was administered with a positive pressure Connell appartus. A curvilinear incision was made on the posterior portion of the right side of the chest (fig. 31), extending from the level of the fifth rib downward and outward to the level of the tenth rib on the posterior axillary line. The ninth rib was excised from its angle forward to the breast and ½ inch (1.27 cm.) was removed from the eighth and tenth ribs in the region of their necks. The pleura was opened in the bed of the ninth rib, and the wound was spread

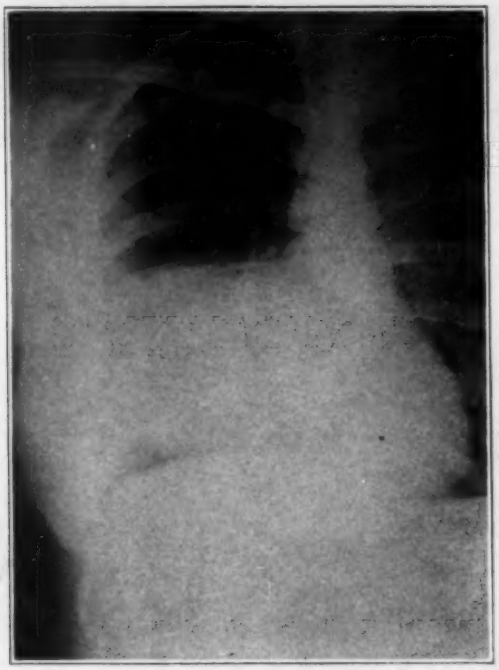

Fig. 30 (case 21).—Roentgenogram of the chest showing a large, round neurofibroma projecting into the right pleural cavity. The tumor arose from the eighth intercostal nerve.

Fig. 31 (case 21).—Postoperative photograph of a patient, indicating the position of surgical incision in removing a tumor of the eighth intercostal nerve. (Compare with figure 30.)

wide open. There was a firm, round tumor with a sessile base attached to the posterior wall of the thoracic cage, arising from the eighth intercostal nerve. The middle lobe of the right lung was adherent to the tumor, but this was readily separated by blunt dissection. The pleural covering of the tumor was then broken into, and the mass was removed by finger dissection after its blood supply had been ligated from the eighth intercostal vessels. Just before the last stitch in the pleural opening was tightened the lung was expanded by positive tracheal pressure, and all air was thus forced out of the pleural sac.

Result.—The patient made an excellent recovery; she has been free from complaint and evidence of recurrence for three years after operation.

Pathologic Examination.—The tumor weighed 326 Gm. and measured 8.8 by 7.6 by 7.8 cm. It was firm, well encapsulated and smooth. The cut surface was heterogeneous and gelatinous. Solid tissues were intermingled with small cavities, from 1 to 3 mm. in diameter, which were filled with a clear, watery fluid.

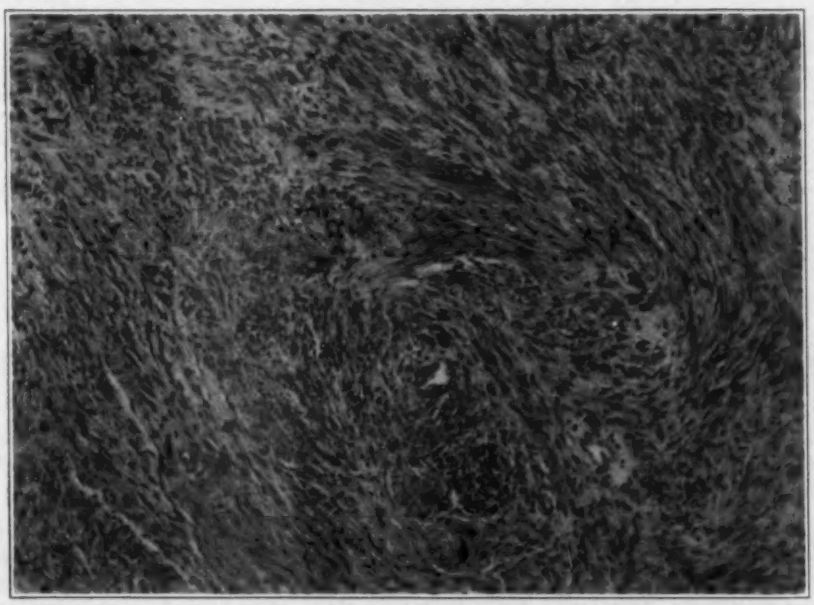

Fig. 32 (case 21).—Photomicrograph (× 110) of a neurofibroma of the intercostal nerve with interlacing fasciculi and whorls of mature connective tissue cells and fibers.

Microscopically, the tumor was fairly cellular and was typical of a neurofibroma. The cells were of a mature type and were arranged in bands and interlacing bundles (fig. 32). There was little variation in size and staining properties of the nuclei. Only slight tendency toward palisading of nuclei was present. Scattered areas showed considerable edema and degenerative change.

Case 22.—F. C., a 30 year old woman, was first seen on Oct. 29, 1921, complaining of gradually increasing pain and swelling in the right axilla of twenty-one months' duration. During the last seven months the pain had radiated down the extensor surface of the arm, over the dorsa of the third, fourth and fifth fingers, to the right breast and also to the region of the scapula. Examination showed a

nodular mass, the size of a hen's egg, in the posterior portion of the right axilla, deeply situated and attached to the under-surface of the scapula, just above its inferior angle.

Operation.—An incision was made along the posterior axillary line and continued at right angles toward the midline of the back. The tumor was growing in the serratus magnus muscle, apparently arising from the long subscapular nerve. There was a forward extension of the mass toward the wall of the chest, so that the fifth rib had to be denuded of its periosteum in removing all of the visible growth. The lower portion of the scapula, the underlying mass and the adjacent musculature were all resected *en masse*. The subscapularis and infraspinatus muscles were then sewed together over the cut edge of the scapula, and the stump of the muscles was then sewed to the cut edge of the latissimus dorsi.

Result.—The patient received postoperative roentgen irradiation over the operative site. She was temporarily relieved, but there was recurrence of pain beginning six months after operation. Five years later the neoplasm had infiltrated the brachial plexus and greatly invaded the upper portion of the thoracic cage. The patient was subsequently lost track of but died in another hospital in May 1934, after exhibiting massive extension of the neoplasm into the brachial plexus and thoracic cavity.

Pathologic Examination.—The nonencapsulated tumor, measuring 7 by 2.5 by 2 cm., infiltrated the adjacent musculature. It was firm and on cross-section presented a light gray substance composed of dense interlacing bands of fibrous tissue.

Microscopically, there were elongated spindle cells in interlacing bundles, cut at different angles. The nuclei were long, ovoid and vesicular and had one or two small nucleoli. Mitotic figures were fairly easily found. The scanty cell cytoplasms trailed out into fine fibrillar structures. The growth had the general appearance of a slowly growing fibrosarcoma, but because of the tendency toward waviness of cells and a suggestion of palisading it was definitely felt to be a malignant tumor of the nerve sheath. The degree of malignancy was insufficient to allow it to be termed a neurofibrosarcoma, but because of the increased rate of growth and subsequent regional extension seen clinically, we have called this tumor a malignant neurofibroma.

Case 23.—R. L. A., a 41 year old woman, entered the hospital on Jan. 8, 1917, complaining of a tender, small lump in the perineum, which had gradually increased in size over a period of seven years. Just to the right side of the central point of the perineum there was a small, firm, tender mass from 2 to 3 cm. in diameter. It did not bulge into the vagina or rectum.

Operation.—Operation disclosed irregular, chainlike, firm and encapsulated masses partly on and partly beneath the deep fascia. These masses were easily dissected free from the surrounding tissues. Small strands of nerve (perineal) were noted entering and leaving these.

Result.—When the patient was last seen, in 1930, there was no evidence of recurrence.

Pathologic Examination.—The specimen consisted of five small discrete circumscribed tumors arranged in a chain and held together by a nerve trunk which passed between them. The largest of these measured 3 by 1.5 by 0.8 cm. On section they were gray and slightly moist, and each was surrounded by a thin capsule.

Microscopic examination of all these masses showed them to be histologically of similar tissue and all representing typical neurofibromas. At the periphery of

the nodules some nerve fibers of the nerve trunks connecting these masses could be identified, but there was no evidence of Recklinghausen's disease.

CASE 24.—A. K., a 32 year old man, was seen on Oct. 17, 1932, having had a hard, superficial, flattened, nontender mass on the midposterior region of the right thigh for six years.

Operation.—An elliptical portion of skin, including the central mass, was excised.

Result.—The patient was not followed.

Pathologic Examination.—In the center of the portion of skin was an area 1.5 cm. in diameter which was raised 0.5 cm. above the level of the surrounding surface of the skin. On section this central pearly white mass was seen to be 1.2 cm. in thickness. It was nonencapsulated but was covered externally by the epidermis and projected down into the subcutaneous fat.

Microscopic examination showed a typical neurofibroma lying in and partially replacing the corium, with interlacing bundles and whorls of mature connective tissue cells laying down a moderate amount of collagen. There was little palisading of nuclei. Small nerves were seen coursing at the periphery of the nonencapsulated tissue.

CASE 25.—W. P., a 33 year old man, was seen in July 1933, complaining of a small, tender lump in the skin over the lateral aspect of the upper part of the left arm, which had been present for several years.

Operation.—A small cutaneous mass with surrounding skin was excised.

Result.—The patient was not followed.

Pathologic Examination.—In the center of the excised skin there was a small, nonencapsulated but fairly discrete mass 5 mm. in diameter, covered externally by epidermis and inferiorly by subcutaneous fat. On cut section this central mass was firm, elastic and pale yellowish gray.

Microscopic examination showed a typical nonencapsulated neurofibroma lying within the corium and replacing the appendages of the skin. It was rather cellular, but there was no evidence of malignancy. Long interlacing bundles and whorl formations were seen, and some mild palisading of nuclei was present. At the periphery of this neurobroma numerous small cutaneous nerves appeared.

SUMMARY

Twenty-five representative cases of benign or malignant tumor of the sheath of a peripheral nerve, unassociated with Recklinghausen's disease, are reported. The most frequent sites for the neoplasms are the posterior surfaces of the legs, the anterior surfaces of the arms and neck. The tumors vary greatly in size and have a marked tendency to cystic degeneration. The benign form is easily separated from the nerve trunk, which can be left intact. The malignant tumor infiltrates and cannot be separated from its nerve. In dealing with the slowly growing neurofibroma, it is justifiable to peel it off from the nerve, but with those showing a more rapid rate of growth a portion of nerve should also be resected, followed by end to end suture of the nerve. Operations on sarcoma of the nerve sheaths should be radical, and in the absence of metastases, early amputation of the involved limb gives the best chance of cure. Radium or roentgen irradiation of the malignant forms has been almost universally a disappointing procedure.

EFFECT OF POSTERIOR PITUITARY EXTRACTS ON MOTILITY OF THE GASTRO-INTESTINAL TRACT

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The numerous attempts to determine the effect of extracts of the posterior lobe of the pituitary gland on the motility of the gastro-intestinal tract have occasioned conflicting and contradictory observations. Having at our disposal a number of patients and several trained dogs with intestinal fistulas, we attempted a further elucidation of this problem.

The literature on this subject is extensive and can be summarized only briefly here.

EFFECT OF POSTERIOR PITUITARY EXTRACTS ON EXCISED STRIPS AND ISOLATED SEGMENTS OF THE INTESTINE

Whereas one might suspect a priori that the effect of posterior pituitary extracts on extirpated intestinal strips could be easily determined, in actual practice the problem is far from solved.[1]

The species of the experimental animal,[2] the p_H of the bath,[3] the presence of histamine or other impurities,[4] and the depressor antiseptics

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Several preliminary experiments were done by Dr. E. Rosenman.

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Aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Geiling, E. M. K.: The Pituitary Body, Physiol. Rev. **6**:62, 1926. Trendelenburg, P.: Die Hormone: Ihre Physiologie und Pharmakologie, Berlin, Julius Springer, 1929, vol. 1, p. 150.

2. Sollmann, T. H.: Glandular Therapy: Pharmacology of the Pituitary Gland, J. A. M. A. **83**:1683 (Sept. 13) 1924.

3. Gruber, C. M.: One of the Factors Governing the Relaxation of Non-Striated Muscle (Intestine) by Commercial Pituitary Extract, J. Pharmacol. & Exper. Therap. **30**:73, 1927.

4. Kaufmann, M.: Ueber die Darmwirkung der Auszüge des Hypophysenhinterlappens, Arch. f. exper. Path. u. Pharmakol. **120**:322, 1927.

contained in commercial extracts [5] serve to explain the varying and contradictory results.

Further, it has been reported that the oxytocic principle of the pituitary gland counteracts the pressor hormone [6] and that the degree of tonus of the intestine determines the type of reaction.[7]

REVIEW OF EXPERIMENTAL WORK REPORTED IN THE LITERATURE

Cat.—Of one hundred anesthetized or pithed cats that received injections of solution of posterior pituitary, some of which were given hourly administrations of the drug for an entire day, only two defecated.[8] Other workers have stated that no augmented colonic activity could be detected fluoroscopically in cats in response to posterior pituitary extract.[9]

Rabbit.—The rabbit is the only animal in which most observers have detected increased peristalsis or defecation.[10] However, inhibition has been reported.[11]

Dog.—Inhibition: The various descriptions of the intestinal response of the dog to posterior pituitary preparations are largely inconsistent.

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5. Roth, G. B.: Pituitary Standardization: The Relative Value of Infundibular Extracts Made from Different Species of Mammals and a Comparison of Their Physiological Activity with That of Certain Commercial Preparations, United States Public Health Service, Hygienic Laboratory, Bulletin 109, December 1916.

6. Elmer, A. W.; Ptaszek, L., and Scheps, M.: Die Wirkung des Vasopressins und Oxytocins auf die Behandlung der Darmlähmung (Ileus Paralyticus) mit Vasopressin, Klin. Wchnschr. **9**:1765, 1930.

7. Gruber, C. M., and Pipkin, G.: Further Observations on the Effect of Pituitary Extract and Morphine Sulphate upon Excised Dog's Intestine, J. Pharmacol. & Exper. Therap. **38**:401, 1930.

8. MacDonald, A. D.: The Action of Pituitary Extracts on Intestinal Muscle, Quart. J. Exper. Physiol. **15**:191, 1925.

9. Brunner, T., and Weigand, W.: Untersuchungen über die Wirkung einiger Peristaltik anregender Mittel, Klin. Wchnschr. **8**:1115, 1929.

10. (*a*) Fodera, F. A., and Pittau, L.: Studi sull'hypophysis cerebri, Pathologica **1**:269, 1909. (*b*) Franchini, G.: Die Funktion der Hypophyse und die Wirkungen der Injektion ihres Extraktes bei Tieren, Berl. klin. Wchnschr. **47**:670, 1910. (*c*) Bell, W. B.: The Pituitary Body and the Therapeutic Value of the Infundibular Extract in Shock, Uterine Atony and Intestinal Paresis, Brit. M. J. **2**:1609, 1911. (*d*) Ott, I., and Scott, J. C.: Action of Animal Extracts upon Intestinal Movements, Am. Med. **17**:154, 1911. (*e*) Katsch, G., and Borchers, E.: Beiträge zum Studium der Darmbewegungen, Ztschr. f. exper. Path. u. Therap. **12**:277, 1913. (*f*) Zondek, B.: Der Einfluss des Hypophysenextraktes auf die Peristaltik, Arch. f. d. ges. Physiol. **180**:38, 1920. (*g*) Gaddum, J. H.: Some Properties of the Separated Active Principles of the Pituitary (Posterior Lobe), J. Physiol. **65**:434, 1928.

11. Shamoff, V. N.: Concerning the Action of Various Pituitary Extracts upon the Isolated Intestinal Loop, Am. J. Physiol. **39**:268, 1916.

More observers have perceived inhibition of the intestine in response to solution of posterior pituitary or pitressin in unanesthetized,[12] anesthetized[13] or pithed dogs[14] and in dogs with intestinal obstruction.[15] Again, the hyperperistalsis evoked by insulin has been reported as being inhibited by the several extracts of the posterior lobe of the pituitary gland.[16]

Dog.—Stimulation: The minority of workers describe excitation of the bowel in response to posterior pituitary extract, but the type of excitation produced has varied distinctly and has apparently been determined in some measure by the presence or absence of anesthesia.

In anesthetized dogs different observers have reported (*a*) an increase in the tonus of the small intestine but a decrease in the tonus of the large bowel[13b] and (*b*) pure excitation.[6]

In unanesthetized dogs with fistulas, solution of posterior pituitary, pitressin and pitocin have evoked a transient diminution in tonus and contraction of the ileum, succeeded by high tonus and intensified peristalsis and occasionally by actual tetanus.[17] Carlson[18] has described an initial augmentation of the hunger contractions. It is particularly interesting that in the unanesthetized dog the pressor and the oxytocic principles have been reported as provoking defecation, fluoroscopy

12. Ginsburg, H., and Tumpowsky, I.: Contributions to the Physiology of the Stomach: I. Studies on the Control of Hunger by Drugs, Arch. Int. Med. **22**:553 (Nov.) 1918. Quigley, J. P.; Highstone, W. H., and Ivy, A. C.: Action of Morphine, Papaverine, Atropine, Pilocarpine, Pituitrin and Pitressin on Intestinal Propulsive Activity Determined in the Unanesthetized Dog by the Bolus Method, J. Pharmacol. & Exper. Therap. **51**:308, 1934.

13. (*a*) Dale, H. H.: The Action of Extracts of the Pituitary Body, Biochem. J. **4**:427, 1909. (*b*) Dixon, W. E.: Pituitary Secretion, J. Physiol. **57**:129, 1923. (*c*) Carlson, H. A.: Effect of Posterior Pituitary Lobe Extracts on the Intestine of Man and Animals, Proc. Soc. Exper. Biol. & Med. **27**:777, 1930. (*d*) Ochsner, A. O.; Gage, I. M., and Cutting, R. A.: The Value of Drugs in the Relief of Ileus, Arch. Surg. **21**:924 (Dec.) 1930.

14. Hoskins, R. G.: Action of Pituitary Extract, J. A. M. A. **66**:733 (March 4) 1916.

15. McIntosh, C. A., and Owings, J. C.: The Effect of Solutions of Pituitary and Various Drugs on the Movements of the Small Intestine During Simple Mechanical Obstruction, Arch. Surg. **17**:996 (Dec.) 1928. Ochsner, Gage and Cutting.[13d]

16. Quigley, J. P., and Barnes, B. O.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: VI. Antagonistic Action of Posterior Pituitary Lobe Preparations, Am. J. Physiol. **95**:7, 1930.

17. Gruber, C. M., and Robinson, P. I.: The Influence of Pituitary Extract, Vasopressin and Oxytocin upon the Intact Intestine in Unanesthetized Dogs, J. Pharmacol. & Exper. Therap. **36**:203, 1929.

18. Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916.

demonstrating an increased motility of the intestinal tract (only with the pressor substance) which could not be detected by the balloon method.[19]

Man.—Most of the data pertinent to man have been gathered by surgeons, since solution of posterior pituitary and pitressin are used widely in the treatment of paresis of the intestinal tract.

The isolated human appendix is reported to undergo an increase in tone on the addition of pituitary extract to the tissue bath.[20] In normal man the reported observations vary from an inconstant gastric motor response and either no effect on or relaxation of the intestines [21] to a distinct increase in peristalsis.[6]

Patients on whom colostomy or ileostomy has been performed have been reported to respond to the subcutaneous injection of pituitary extracts with an increase in the intestinal activity.[13c]

In the presence of atony of the intestinal tract, solution of posterior pituitary or pitressin may yield borborygmi, release of flatus and defecation.[22] Other surgeons have described an increase in tone and no stimulation of peristalsis as the effect of the drugs.[23]

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19. Melville, K. I., and Stehle, R. L.: The Actions of Pituitary Preparations (Posterior Lobe) upon the Intestines of the Dog, J. Pharmacol. & Exper. Therap. **50**:165, 1934.

20. Cross, D. G. T. K.: The Action of Physostigmine and Pituitrin, Brit. M. J. **1**:9, 1924.

21. Pancoast, H. K., and Hopkins, A. H.: The Action of Pituitrin upon the Gastro-Intestinal Tract of Man, New York M. J. **105**:289, 1917.

22. Bidwell, L. A.: Investigation into Effect of Pituitary Extract on Bowels After Abdominal Operations, Clin. J. **38**:351 (Sept. 6) 1911. Klotz, R.: Pituitrintherapie bei Peritonitis, München. med. Wchnschr. **59**:2047, 1912. Houssay, B. A., and Beruti, J.: Sur l'emploi de la médication hypophysaire comme agent entérocinétique, Presse méd. **21**:613, 1913. Duffy, R.: Pituitary Extract in Post-Operative Intestinal Stasis, New York M. J. **101**:72, 1915. Young, H. H.: The Value of Drugs in Urology, J. A. M. A. **77**:1327 (Oct. 22) 1921. Pate, J. C.: The Use of Pituitrin in Abdominal Surgery, J. M. A. Georgia **11**:455, 1922. Mayer, A.: Zur Behandlung postoperativer Darmlähmungen, München. med. Wchnschr. **71**: 931, 1924. Schmidt, H.: Vergleichende Untersuchungen über die Darmwirkung des Hypophysins, Zentralbl. f. Chir. **52**:121, 1925. Vogt, E.: Die intravenöse Hypophysinkochsalzinfusion zur Behandlung der postoperativen Darmlähmung, München. med. Wchnschr. **73**:1509, 1926. Ward, G. G.; Lyon, E. C., and Bemis, G. G.: Clinical Results Obtained with Oxytocin and Vasopressin, the Recently Isolated Principles of Pituitary Extract, Am. J. Obst. & Gynec. **16**:655, 1928. Black, C. V.: Pitressin in Surgery, J. Kansas M. Soc. **35**:216 (June) 1934. Fervers: Hyphophysenextrakt-Injektion bei Ileus und nach Laparatomie, Med. Klin. **18**:438, 1922. Elmer, Ptaszek and Scheps.[6] Bell.[10c]

23. Potter, P. C.: The Relation of Post-Operative Paralytic Ileus to Mortality in Acute Appendicitis, Ann. Surg. **99**:985, 1934; Acute Diffuse Peritonitis Following Acute Appendicitis with a Report of Twenty-Five Cases, S. Clin. North America **14**:379 (April) 1934. Potter, P. C., and Muller, R. S.: Posterior Pituitary Extract in the Prevention of Post-Operative Intestinal Distention, Ann. Surg. **86**:364, 1932.

Pituitary extracts have been employed successfully in the treatment of constipation.[24]

In a case of poisoning due to the ingestion of chenopodium, intravenous administration of 600 cc. of saline solution plus six ampules of pituitary extract induced defecation.[25]

Cushing [26] reported an increase in the tone of the gastro-intestinal tract and violent contractions after the intraventricular administration of solution of posterior pituitary double U. S. P. strength, and a diminution in tone after intravenous injection.

METHODS

The balloon method of Carlson [18] and recording water manometers were used. The patient lay comfortably in bed, with a signal button in hand to indicate pain, hunger, etc. Pitressin, pitocin and solution of posterior pituitary were the drugs used, the injections being given intramuscularly.[27]

Dogs with gastro-intestinal fistulas were selected for their docility and training. They lay quietly on a soft pad, with eyes blindfolded, for several hours, undisturbed by intravenous or intramuscular injections.

Since it has been thought possible that diet may influence the response of the organism to the extract,[28] dog 1 was fed for two weeks a vegetable-carbohydrate diet, a meat-carbohydrate diet and a mixed diet, respectively. With this exception, all other tests involved no dietary restrictions.

The acute experiments on the dog were performed with the animal under ether anesthesia (one under narcosis with pentobarbital sodium). Blood pressure was recorded with a mercury manometer; the motility of the gastro-intestinal tract with balloons and water manometers.

In several acute experiments on animals, a one stage bilateral adrenalectomy was performed, and of these experiments none is included here in which the blood pressure sank below 80 mm. of mercury.

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24. Sophian, A.: Pituitary Extract (Posterior Lobe), J. Missouri M. A. **27**:384, 1930. Carnot, P., and Terris, E.: Action des extraits post-hypophysaires sur le peristaltisme intestinal et sur la constipation, Paris méd. **1**:333, 1926.

25. Vogt, E.: Ueber die Verwendung der intravenösen Hypophysenkochsalzinfusion bei der Behandlung der Vergiftungen durch Oleum chenopodii, Klin. Wchnschr. **5**:1638, 1926.

26. Cushing, H.: Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 106.

27. The pitressin and pitocin were supplied by Parke, Davis & Co., the solution of posterior pituitary by Wilson Laboratories and the solution of posterior pituitary double U. S. P. strength by Eli Lilly & Co.

28. Abderhalden, E., and Wertheimer, E.: Studien über den Einfluss der Ernährung auf die Wirkung bestimmter Inkretstoffe, Arch. f. d. ges. Physiol. **205**:559, 1924; **206**:451, 1924; **207**:222, 1925; **213**:328, 1926. Degener, L. M.: Studies on the Effect of Diet on the Weight of the Hypophysis and Thyroid Gland of the Albino Rat, and on the Action of Their Extracts on the Isolated Small Intestine, Am. J. Physiol. **60**:107, 1922.

RESULTS

Man (table 1).—Sixteen tests were performed on ten subjects. Nine of the patients had an intestinal fistula, and one subject was a normal young woman. All were in excellent physical condition at the time of the tests, their respective operations having been completed months, and in some instances years, before. Those on whom resection for colonic carcinoma had been performed may have had metastases at the time of these experiments, but, clinically and subjectively, their condition was good. In the patients with ulcerative colitis, either the diseased segment of bowel had been extirpated or a simple ileostomy had allayed symptoms. The balloon was passed along the fistula into the uninvolved portion of the intestine and held in place by adhesive tape attached to the skin.

Table 1 indicates that the human ileum was inhibited by pitressin only once. In ten tests pitressin augmented the tonus of the ileum or colon, and in three other instances it elicited no response.

The change in the amplitude of the contractions of the intestine paralleled the alteration in tone. Thus, in twelve trials, ileal and colonic contractions were considerably increased by pitressin, and in only one case was this effect not obtainable.

The stomach of the normal subject (no. 10) failed to respond in any way to pituitary extract in the doses employed.

Particularly significant is the datum that in six tests pitressin caused colicky pain.

In several instances pitressin elicited maximal intestinal contractions, which at least once culminated in subtetanus of the ileum (no. 6). Further, moderately high contractions appeared in another four tests.

The latent period was usually short: from one tenth of a minute to thirteen minutes, with an average of five minutes. The duration of contractions induced by pitressin varied from six to thirty minutes. In four subjects powerful contractions extruded the balloon from the fistula. Occasionally the experiments were interrupted because of discomfort of the patient. Defecation occurred through the stoma nine times in fourteen trials. In one patient evacuation of the bowel in response to pitressin occurred five times in the course of one experiment and again three times at a subsequent examination.

Chart 1 depicts the result of the first test on patient 8 (table 1). It demonstrates the strong intestinal contractions produced by 0.5 cc. of pitressin administered intramuscularly, which expelled the balloon from the fistula and terminated in defecation.

Throughout the latent period, the tonus and motility of the colon were depressed, and after the period of specific response this condition reappeared. This was commonly observed in the majority of the experiments in man and in the dog in which pitressin produced a motor effect.

The short and transient contraction, on reintroduction of the balloon, results from the initial distention of the intestine. For this reason, every injection of a drug was preceded by a control period of not less than thirty minutes. When no regularity in motility was observed, resort was taken to longer control periods, or occasionally the particular experiment was abandoned.

Unanesthetized Dogs.—Three dogs were used, all manifestly in excellent health. Dog 1 was served in succession a vegetable, a meat and a mixed diet, as described previously, but the individual results of these periods are not recorded separately, since no significant differences were obtained.

TABLE 1.—*Results of Motor Response of the Intestines to Pitressin*

Patient				Location of Fistula in	Disease	Pitressin, 1 Cc. Intramuscularly	Before Injection		After Injection					
											Tonus and Contraction, Min.			Defecation, Minutes After Injection
No.	Initials	Sex	Age				Tonus	Contractions	Tonus	Contractions	Latent Period	Duration	Pain	
1	A. L.	F	34	Ileum	Ulcerative colitis	0.5	Small waves	Small	Increased	Maximum	2	29	Cramplike	13
2	B. S.	M	27	Ileum	Ulcerative colitis, colectomy	1.0	Small waves	Small	Slight decrease	Slight decrease	2	30	..	..
3	H. K.	M	25	Ileum	Ulcerative colitis	1.0	No waves	None	Increased	Maximum	5	30	..	15
						1.0	Small waves	Small	Increased	Medium	13	Balloon out	..	13
4	B. D.	M	16	Ileum	Ulcerative colitis	1.0	No waves	Small	Waves	Medium	3	20 Test ended	..	..
						1.0	No waves	Small	No waves	Small	..	..	..	..
5	N. G.	F	22	Ileum	Ulcerative colitis	1.0	No waves	Small	No change	Medium	3	25 Test ended	..	8
6	G. I.	M	65	Ileum	Cancer of rectum	1.0	Medium waves	Medium	No change	At first, medium, then subtetanic	7	35 Test ended	..	18-21-25-29-35
						1.0	Small waves	Small	Increased	High	13	16	Colicky	15-17-21
7	R. T.	M	60	Colon	Cancer of rectum	0.5	Medium waves	Medium	Increased	Maximum	1/10	Balloon out	+++	2
8	L. D.	M	43	Colon	Cancer of rectum	0.5	Small waves	Small	Medium waves	High	5	Balloon out	++	..
						1.0*	Small waves	Small	Medium waves	High	7	6	..	..
9	L. L.	F	30	Colon (sigmoid)	Ulcerative colitis	0.5	No waves	Medium	Increased	Maximum	3	Balloon out	+++	4
						0.5	No waves	Small	Increased	High	5	25 Test ended	+++	14
10	D. M.	F	21	Stomach balloon swallowed	Normal student	1.0	Small waves	Small	Small waves	Small	..	..	..	..
						1.0	Small waves	.....	Small waves	.....	..	..	..	..

* Solution of posterior pituitary; Parke, Davis & Co.

In this dog, pitressin and pitocin either decreased the tone and the amplitude of the contractions of stomach and jejunum or had no effect. Only once was a slight rise of gastric tonus observed (solution of posterior pituitary). The latent period for depression varied between one and eight minutes (once twenty minutes), with an average of three and one-half minutes. The duration of the depression varied from eleven to forty-five minutes, averaging twenty-one minutes.

However, in one test, after the use of surgical solution of posterior pituitary double U. S. P. strength the stomach underwent complete inhibition of tonus and motility for sixty minutes and complete inhibition of hunger contractions for one hundred and twenty minutes (a total of three hours). At the time of injection, hunger contractions prevailed. From a two months' study of this dog's hunger contractions, we knew their periodicity, and no period of relative quiescence between hunger contractions ever lasted longer than thirty minutes.

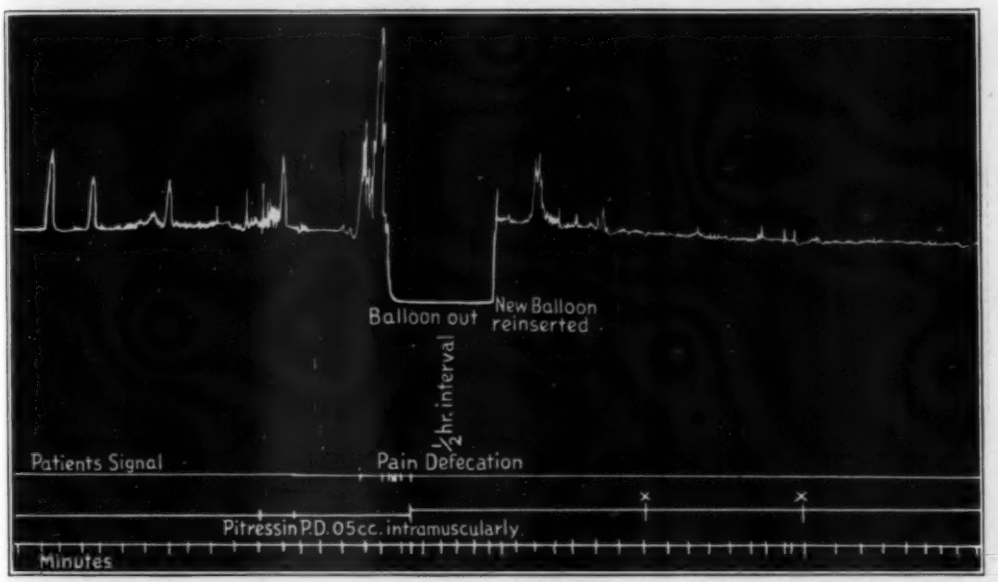

Chart 1.—Response of human colon to intramuscular injection of 0.5 cc. of pitressin.

In general, both the stomach and the jejunum behaved identically as to the latent period and the duration of the response.

Dogs 2 and 3 received only pitressin.

Dog 2 received seven injections of the drug, three proving entirely negative in effect, whereas the other four evoked ileal depression (latent period, from one to three minutes; duration, from eleven to nineteen minutes).

Dog 3 was easily the most placid and docile of the three animals. Here every experiment, although not every injection, yielded a distinct and frequently marked increase in tonus and in the number and height of contractions.

In this dog, six of eight injections of pitressin produced positive motor effects in the stomach and ileum (latent period, from one to eight minutes; duration, from four to thirty-two minutes). This animal was the only one that defecated in response to pitressin (four times).

In most instances a depression of motility and frequently of tonus appeared during the latent period. In three experiments tetanic contractions of the ileum developed, succeeded by strong contraction waves, which then passed into a long period of depression or complete inhibition of motility and tonus. Chart 2 illustrates a typical experiment with this dog.

We considered it especially significant that pitressin consistently stimulated the motility of the gastro-intestinal tract in only dog 3, which was so thoroughly unruffled that even defecation or disturbances in the room about her constituted insufficient reason for movement.

The other two dogs, although well trained and quite unmindful of the intravenous injections, could be disturbed by extraneous noise. And thus the possibility was suggested that at least some component of the inhibition induced by pitressin in these dogs might represent sensory or adrenal inhibition.

Accordingly, the investigations were extended to include eight etherized dogs and four acutely adrenalectomized dogs.

Anesthetized Dogs.—In this group, forty-six injections of pitressin yielded increased tonus and in the height of the contractions of the stomach, jejunum, ileum or colon (seven times); depression of tonus and amplitude of the contrac-

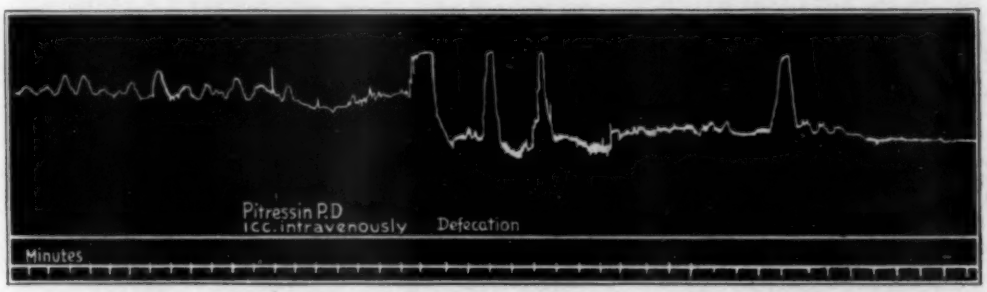

Chart 2.—Response of ileum of dog no. 3 to intravenous injection of 1.0 cc. of pitressin.

tions (seven times), and no effect (thirty-two times). Pitocin and solution of posterior pituitary were entirely ineffectual, never eliciting the depression that sometimes occurred in unanesthetized dogs.

Unlike the response of the unanesthetized dogs (nos. 1 to 3, table 2), the stimulating effect obtained here with pitressin did not occur consistently in any one dog or in any segment of bowel. A casual comparison of these data with the response of the unanesthetized dogs 1 and 2 indicates that the gastro-intestinal tract of the narcotized dog responded more frequently to pitressin with an increase in tonus and contractions.

Adrenalectomized Dogs.—Pitressin had practically no effect on the adrenalectomized animals. Their gastro-intestinal tract remained atonic, the result possibly of the section of many sympathetic fibers and trauma to the celiac ganglion during adrenalectomy.

COMMENT AND CONCLUSIONS

The consistency with which pitressin is effective in producing an increase in the intestinal activity in man is remarkable. The response in dogs is hardly as unequivocal.

TABLE 2.—*Experiments on the Motility of the Stomach and Intestine (Balloon Method)*

Dog					Number of Observations on						
					Increase of			Decrease of			
No.	Sex	Weight, Kg.	Position of Balloon	Drug Injected (1 Cc. Intramuscularly)	Tonus	Contractions	Tonus and Contractions	Tonus	Contractions	Tonus and Contractions	No Effect
				A. Normal Unanesthetized Dogs							
1	F	29	Stomach	Sol. of post. pituitary	(1)*	..	..	1	..	1	11
				Pitressin	..	..	..	..	..	..	6
				Pitocin	..	..	..	..	..	2	..
			Jejunum	Sol. of post. pituitary	..	..	..	..	..	1	3
				Pitressin	..	..	..	2	..	3	2
				Pitocin	..	..	..	1	..	..	1
				1 Cc. Intravenously							
2	F	19	Ileum	Pitressin	..	..	..	3	..	1	3
3	F	19	Stomach	Pitressin	1	..	..	..	..	1	..
			Ileum	Pitressin	..	..	5	..	..	..	1
				B. Dogs Under Ether Anesthesia							
4-11	4 F, 4 M	10-14	Stomach	Pitressin	..	2	..	1	..	..	6
				Pitocin	..	..	..	..	..	..	2
			Jejunum	Pitressin	..	(1)*	..	..	1	..	6
				Pitocin	..	..	..	..	..	..	2
			Ileum	Sol. of post. pituitary	..	..	..	..	..	..	2
				Pitressin	..	..	2	3	1	..	10
			Colon	Sol. of post. pituitary	..	..	..	..	..	..	2
				Pitressin	..	..	2	1	..	..	10
				Pitocin	..	..	..	..	..	..	2
				C. Dogs Under Ether Anesthesia; After Bilateral Adrenalectomy							
12-15	2 M, 2 F	10-17	Stomach	Pitressin	..	1	..	..	..	..	4
			Ileum	Pitressin	..	..	..	..	..	..	11
			Colon	Pitressin	..	..	..	1	..	..	10

* The parentheses indicate that the increase of tonus or contractions was slight.

However, it was demonstrated that in a well trained and especially placid dog (no. 3, table 2) pitressin evoked the same response as in man: a marked increase in tonus and in the height and frequency of the contractions, tetanus and defecation. The other two dogs (nos. 1 and 2) were certainly well trained but more easily perturbed by external movements and noise, and for them pitressin proved to be ineffectual. This may indicate that the susceptibility of a dog to external disturbing stimuli may modify the action of the drug.

The experiments performed with the dogs under ether anesthesia (table 2, no. 4 to 11) partly corroborate this assumption, because here the incidence of a positive response of the gastro-intestinal tract to pitressin was greater than that which occurred in the unanesthetized dogs. (nos. 1 and 2).

The experiments on adrenalectomized dogs do not demonstrate much. The trauma to the celiac plexus and to the sympathetic fibers may partly explain the negative results. Hoskins and McPeek,[29] in an attempt to determine the relationship between the pressor effect of solution of posterior pituitary stimulation of the adrenal glands, reached a similar conclusion. Yet it should be remembered that many other stimuli may inhibit the canine intestine, and therefore a number of well conceived experiments will be necessary to solve this problem.

The foregoing results in man demonstrate that pitressin (solution of posterior pituitary in one subject) consistently evokes the motility of the intestinal tract and frequently elicits violent contractions, tetanus, colicky pain and defecation. This confirms recent work performed on a smaller group of patients.[13e]

The slow, tonic contractions of the intestine observed by surgeons [23] when solution of posterior pituitary was given in the course of a laparotomy were never visible in our records. Possibly such results depend on the acute surgical procedure as well as on the handling of, and the access of cool air to, the viscera.

In all experiments on man and on the dog we were unable to detect a constant correlation between the preceding state of tonus and contractions and the response to the extracts of the posterior lobe of the pituitary gland. Nor could we establish the existence of an antagonism between pitressin and pitocin.

In view of our data, it is somewhat difficult to interpret the failure of fluoroscopy to detect motility.[21] Of course we are aware of the profound differences between the balloon method and fluoroscopy. But, if anything, the former method is less sensitive and gives less information

29. Hoskins, R. G., and McPeek, C.: Is the Pressor Effect of Pituitrin Due to Adrenal Stimulation? Am. J. Physiol. **32**:241, 1913.

than the latter, so that positive results obtained with the balloon method are therefore particularly significant (Carlson).[16]

The violent contractions in several experiments in which only 0.5 cc. of pitressin was given intramuscularly (table 1, patients 1, 7, 8 and 9) warn the surgeon to be cautious in the use of this drug, particularly in those instances in which the intestinal wall may be weakened. A strong contraction or tonus wave from the unaffected bowel above the lesion may push fluid into the diseased portion and produce a perforation. It is suggested, therefore that subcutaneous injection of small doses of pitressin is indicated.

SUMMARY

The pressor, oxytocic and mixed principles of the posterior lobe of the pituitary gland, in the form of pitressin, pitocin and solution of posterior pituitary, were injected into man and dogs with balloons at various levels of their gastro-intestinal tract.

Nine subjects with ileal or colonic fistulas and one normal young woman who swallowed a stomach balloon were tested.

Of the nine patients with fistulas, eight responded to the drugs with increase in tonus and in the amplitude and height of the contractions. Violent contractions, tetanus, colic and defecation occurred in several of the subjects.

Caution appears indicated in the clinical use of pitressin, particularly when the intestinal wall is weakened.

Only one of three normal unanesthetized dogs manifested increased intestinal activity in response to pitressin. Apparently the temperament or disposition of the animal represents a contributing factor.

LEIOMYOMA OF THE STOMACH

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It has been stated that a benign tumor of the stomach occurs so rarely that it may be regarded only as a clinical curiosity. More often it is taught that a tumor of this type is usually asymptomatic and that it is seen as a rule only incidentally at autopsy. A review of the literature, however, shows that, though decidedly infrequent, such a tumor may give rise to grave or persistent symptoms referable to the gastro-intestinal tract. The fact that a new growth of the stomach may be benign assumes a practical aspect in view of the importance of conserving such an organ as the stomach.

My interest in this subject was aroused recently by an unusual case in which severe gastric hemorrhage occurred. As the patient had suffered three attacks of hematemesis, two of which had been so severe as to reduce him to a state of shock, exploration of the gastric region seemed indicated. At operation a small leiomyoma of the stomach was removed, and the patient made an uneventful recovery. A complete report of the case is given here. In this instance the diagnosis of bleeding duodenal ulcer had been made. This error in diagnosis and the realization that the patient might have died at an early age from a remediable pathologic lesion had the surgeon not intervened caused me to make a careful study of the literature pertaining to leiomyoma of the stomach. It was hoped that definite correlation between the clinical and the pathologic picture might be revealed.

Excellent treatises are available on the general subject of benign gastric tumor, and complete monographs have been found dealing both with benign and with malignant tumor of smooth muscle origin occurring in the stomach. The collective papers presented information regarding the frequency of benign gastric tumor and of leiomyoma in particular. Eusterman and Sentry reported 27 cases of benign tumor of the stomach discovered at operation in a period during which 2,168 malignant gastric new growths were found at operation. This represents a proportion of 78 malignant tumors to 1 benign tumor; in other words, benign lesions constituted 1.3 per cent of all gastric tumors. Nadeau and McCarty reported a study of gastric tumors over a period of eight years, of which 1.2 per cent were benign. Lockwood stated

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that 5 per cent of all tumors of the stomach discovered at necropsy or removed at operation are benign. In the series of Eusterman and Sentry, 3 of the 27 benign tumors were leiomyomas. This constitutes 11.1 per cent of all benign gastric tumors. Farr and Glenn stated that myoma is the most important of the benign tumors in respect to frequency and the symptoms to which it gives rise. A study of the separate case reports was made to determine the symptomatology which may be attributed to leiomyoma of the stomach. To verify the statements made in the collective reports, the original articles to which they refer have been consulted.[1] In all, 56 cases have been found with sufficiently complete descriptions to establish the fact that the tumor in question was a benign lesion of smooth muscle origin. Twenty-three of these tumors were discovered at operation, and 33 are described in autopsy reports. The diagnosis of leiomyoma has been verified by consulting the microscopic descriptions of the tumors, except in some of the early cases in which the results of the microscopic examination are not recorded. In these, however, the gross pathologic descriptions were so complete that there is little doubt that each case was one of true leiomyoma of the stomach. Cases of fibromyoma, adenomyoma, other benign tumors or leiomyosarcoma of the stomach have been excluded from this report. With the addition of my 2 cases, there is, then, a total of 58 cases of leiomyoma of the stomach, in 25 of which the growth was found at operation and in 33 at autopsy. In 1 of the cases reported here the patient was observed and operated on by me; the other case was found in records of the New York Hospital. Twelve cases mentioned by F. Cohen and 5 by Nadeau and McCarty and 19 recorded by Geschickter in which no detailed accounts are given are not included in this paper.

CASES OF LEIOMYOMA DISCOVERED AT OPERATION

Twenty-five cases of gastric tumor are described in the literature in which the growth was clearly a leiomyoma and in which surgical treatment was instituted. My 2 cases are included in this number. In this group a study of the clinical data has been considered of great importance, since the patients presented symptoms of sufficient severity to justify surgical intervention. This is in contrast to the group of cases in which the growth was discovered at autopsy, in the reports of which symptoms often are not given or in which the constitutional changes occurring before death had so masked the clinical picture that the gastro-intestinal symptoms played no prominent rôle.

1. Ninety-eight original papers have been consulted in this review of the literature. All cases variously reported as instances of leiomyoma in which the diagnosis was doubtful have been eliminated from this discussion.

The earliest case in this group is that of Rupprecht (1890). In his case the tumor, which weighed 251 Gm., was removed by gastric resection; the patient did not survive the operation.

The youngest patient operated on was a 9 year old boy, whose case was reported by Outland and Clendenning. A two stage gastric resection gave an excellent result. The oldest patient coming to operation was a man 78 years of age, whose case was reported by Yates. Partial gastrectomy was followed by recovery.

The age incidence in this group of cases was as follows:

Years	No. of Patients
0-10	1
30-40	4
40-50	9
50-60	3
60-70	4
70-80	1
Age not stated	3

In regard to sex, the occurrence was almost equal; in 22 cases in which the sex is given, 10 patients were males and 12 females.

Information is given in regard to race in only 5 cases; all the patients were Caucasians.

A detailed study of the symptoms, physical signs and gross pathologic picture in these 22 cases in which a leiomyoma of the stomach was found at operation indicates that they may be classified in the following distinct groups:

1. Cases of small leiomyoma which occurs in the region of the pylorus and manifests itself only by the symptoms of pyloric obstruction. In this group there are 8 cases, reported by Herhold, Samter, Peugniez and Jullien (2 cases), Outland and Clendenning, Eusterman and Sentry, Truesdell and me. In all these cases the symptoms were pain in the upper part of the abdomen and vomiting. The tumors are described as small (often referred to as the size of a nut) and located at or near the pylorus. The tumor in my case was 2.5 cm. in diameter. In only 2 cases was the tumor palpable on abdominal examination; in these cases it measured 8 by 6 cm. and 5 by 7 cm., respectively. Peugniez and Jullien described a tumor on the posterior wall, the proximity to the pylorus not being stated. The patient's symptoms were those produced by pyloric obstruction, and as the stomach was found to be dilated at operation the case has been included in this group.

2. Cases of large leiomyoma occurring in the fundus of the stomach and manifesting itself either by symptoms of partial gastric obstruction or by the presence of a palpable tumor. In this group there are 8 cases, reported by Rupprecht, von Erlach, Nicoladini, Goebel, Lowit,

Moura (2 cases) and Emmert. The locations of the tumors were given as follows: at the cardia, on the lesser curvature, on the anterior gastric wall (2 cases) and on the posterior surface of the middle one third of the stomach (2 cases). In two cases the site of the tumor was not indicated.

An idea of the size of the tumors in this group may be gained from the fact that 1 is said to have weighed 251 Gm., another 1,560 Gm. and a third 5,400 Gm. In 5 cases the sizes were variously recorded as "large as a child's head" (Goebel), "large as a man's head" (Lowit), 14 by 26 cm. (Nicoladini), 13 by 7 cm. (Moura) and 8 by 1 cm. (Moura).

In all patients except the last mentioned, an abdominal tumor was palpable. In 5 cases pain was the prominent symptom; consciousness of the tumor was recorded in 1 case, and symptoms were not listed in 1 case.

3. Cases of small leiomyoma at a distance from the pylorus and manifesting itself by severe gastro-intestinal hemorrhage. In this group there are 4 cases, reported by Thompson, Eusterman and Sentry, Eusterman and Balfour and me. The tumors were 2 cm. in diameter, 0.5 by 2 cm. in diameter, 3.5 by 5.5 by 4 cm. and 6 by 4 cm. in size. The weights of the tumors are not recorded. All were distinctly encapsulated lesions. In my case there were definite folds in the mucosa over the tumor, giving the suggestion of the formation of crypts; at one point there was a minute ulceration 3 mm. in diameter (fig. 1). The same type of mucosal crypt formation was seen in Thompson's case, but no ulceration was evident. A photograph of Thompson's specimen is shown in figure 2. He referred to the tumor as a fibromyoma, but the microscopic sections indicate that it was a tumor chiefly of muscle cell origin. The gross pathologic picture so closely resembled that in 1 of my cases that it has been included in the group. All 4 of these patients were subjected to operation because of severe hematemesis or recurring melena. My patient had grave hematemesis, on two occasions so severe as to cause profound shock. The patient of Eusterman and Sentry had symptoms of recurring melena and hematemesis and exhibited marked anemia. The patients of Thompson and of Eusterman and Balfour had recurrent melena and massive gastric hemorrhage.

These patients were 41, 42, 45 and 54 years of age, respectively.

Five cases in which a gastric leiomyoma was discovered at operation fail to fit into any of the foregoing groups. In 3 of the 5 cases neither the symptoms nor the position of the tumor was given. In Eusterman and Sentry's case the tumor was said to have been near the pylorus, and the symptomatology was given as a "duodenal ulcer syndrome."

For lack of more detailed information, this case could not be classified. Yates reported a case in which a small tumor was found on the posterior wall of the stomach. The patient's chief symptom was epigastric distress after meals. A cholecystectomy was done at the time the tumor was removed, and it is possible that the epigastric distress was due to the pathologic process in the gallbladder and that the tumor was asymptomatic. More will be said about the small asymptomatic leiomyoma in the discussion of cases in which the growth was discovered at autopsy.

OPERATIVE TREATMENT; IMMEDIATE AND LATE RESULTS

The operative treatment is recorded in 19 of the 25 cases as follows:

Operation	No. of Cases
Partial gastric resection	4
Partial gastric resection, pyloroplasty	2
Partial gastric resection, cholecystectomy	1
Partial gastric resection, gastro-enterostomy	1
Pylorectomy	1
Pylorectomy, gastro-enterostomy	1
Billroth operation (II)	1
Polya-Mayo's operation	1
Two stage gastric resection	1
Annular gastrectomy	1
Median gastric resection	1
Removal of tumor	3
Exploratory laparotomy, stomach torn, wound packed	1

The patients on whom annular gastrectomy and exploratory laparotomy was performed died after operation. There was also one fatality in the 3 cases in which the tumor was removed. The patient on whom partial resection was done failed to recover.

In only 19 of the 25 cases was the result of operation stated; in 15, or 78.9 per cent, of these recovery followed operation, and in 4, or 21.1 per cent, the patients died. One of the 4 patients died of embolus fifteen days after operation; the second died of peritonitis on the eighth postoperative day; the third died ten months after operation, of complications brought about by complete separation of the wound, and the fourth died a few days after removal of the tumor, the cause of death not being stated. It is to be remembered in evaluating the mortality that of 4 deaths, 2 (Rupprecht and Nicoladini) occurred before the close of the nineteenth century.

Eight patients recovered from operation, but no follow-up report is given. Seven others recovered and were reported as well two months, six months, six months, seven months, and one year, one and one-half year and three years, respectively, after operation.

The 25 cases in which a leiomyoma of the stomach was discovered at operation were described by Rupprecht, von Erlach, Nicoladini, Herhold, Samter, Yates, Goebel, Thompson, Bland-Sutton (2 cases), Peugniez and Jullien (2 cases), Lowit, Outland and Clendenning, Eusterman and Sentry (3 cases), Moura (2 cases), Ungar, Truesdell, Eusterman and Balfour, Emmert and me (2 cases).

The reports of my 2 cases of leiomyoma of the stomach follow:

CASE 1.—F. S., a white man aged 41, was admitted to the surgical service of the New York Hospital in a state of profound shock after sudden hematemesis. The immediate therapy was directed toward the replacement of blood. Subsequently the patient passed a number of copious tarry stools, but his condition gradually improved. After three days of fasting he was given a Sippy diet; this was followed by sudden hematemesis, with the loss of approximately 1 pint (473 cc.) of bright red blood. The patient again went into shock and was desperately ill for four days. He slowly recovered from the profound anemia.

Fig. 1 (case 1).—Leiomyoma of the stomach. Note the thick capsule of the tumor.

The patient stated that for nine years he had had gastric pain after eating, which was usually relieved by taking sodium bicarbonate or food. At another institution he had been placed on a Sippy diet with relief of his symptoms. Three years before admission to the New York Hospital he had an attack which suggested gastric hemorrhage, and serial roentgenograms of the gastro-intestinal tract made by Dr. Arthur L. Holland at this time showed a defect on the lesser curvature, which was thought to represent a gastric ulcer. After dietary therapy this defect disappeared.

The family history was irrelevant save for the fact that the patient's mother died of carcinoma of the stomach.

Physical examination on admission gave negative results, except for the evidences of shock. The patient was a fairly well developed and well nourished man. The pupils reacted normally to light and in accommodation, and the fundi were normal. The blood pressure was 120 systolic and 80 diastolic. The heart and lungs were normal. There was no abdominal tenderness. The liver and spleen were not palpable. The extremities showed no abnormalities.

As soon as the gastric bleeding ceased, serial roentgenograms of the gastro-intestinal tract were made on two occasions. At neither time was anything abnormal seen in the fluoroscopic examination of the stomach and duodenum. A gastric analysis was not done for fear of starting another violent hemorrhage. The Wassermann reaction of the blood was negative.

An exploratory operation revealed a small tumor, measuring 2 by 2 cm., in the wall of the stomach. It was roughly oval and was located on the lesser curvature of the stomach 6 cm. from the pylorus. The gastric serosa overlying the tumor mass appeared to be normal, and when the stomach was opened the mucosa was seen to be intact over it. The tumor presented a hard, encapsulated mass in the gastric wall, apparently not attached to the mucosa or the serosa. A diamond-shaped section of the stomach was excised which included the lesion and a wide margin of normal gastric wall. A posterior gastro-enterostomy was done.

A section of the tumor is shown in figure 1. Gross examination revealed two distinct crypts of the mucosa directly overlying the tumor. A minute ulceration

Fig. 2.—Photograph of the tumor and a portion of the stomach in Thompson's case. The report of Morgan's case shows a photograph of a tumor which has a striking resemblance to this one (Thompson, J. E.: Tr. South. S. Gynec. A. **21**:17, 1909).

of the mucosa, 3 mm. in diameter, also was evident. The cut surface of the specimen was dull grayish white. Dr. N. Chandler Foot described the gross and microscopic appearance of the tumor as follows:

The tumor was definitely circumscribed by a tough brawny white capsule about 4 mm. in thickness, from which it bulged on section. The whole growth was embedded in the muscular portion of the gastric wall and was covered on one aspect by mucosa and on the other by serosa. At one point in the former, over the convexity of the tumor, there was a small ulceration, about 3 mm. in diameter, with a congested base and a slighlty necrotic raised rim. The tumor itself was about 3 cm. in diameter and was set off from the capsule both by its pinker color and by its softer and more meaty consistence. It bulged about the cut surface, was finely lobulated and cut without noticeable resistance; there was no gritty sensation as the knife passed through it.

Microscopic sections showed the tumor to be of unmistakable smooth muscle origin; the cells were poorly matured leiomyoblasts of a type intermediate between the primitive cell seen in the leiomyosarcoma and the more adult form encountered in the leiomyoma. The large ovoid and somewhat hyperchromatic nuclei occupied the middle of the cells and were surrounded by feathery, poorly consolidated masses of smooth muscle. This is well shown in the photomicrograph. Mitotic figures were not found after considerable searching, and there was no marked invasion of the capsule by the growth. For this reason the tumor was classified as a nonmalignant leiomyoma with a very cellular and somewhat anaplastic make-up.

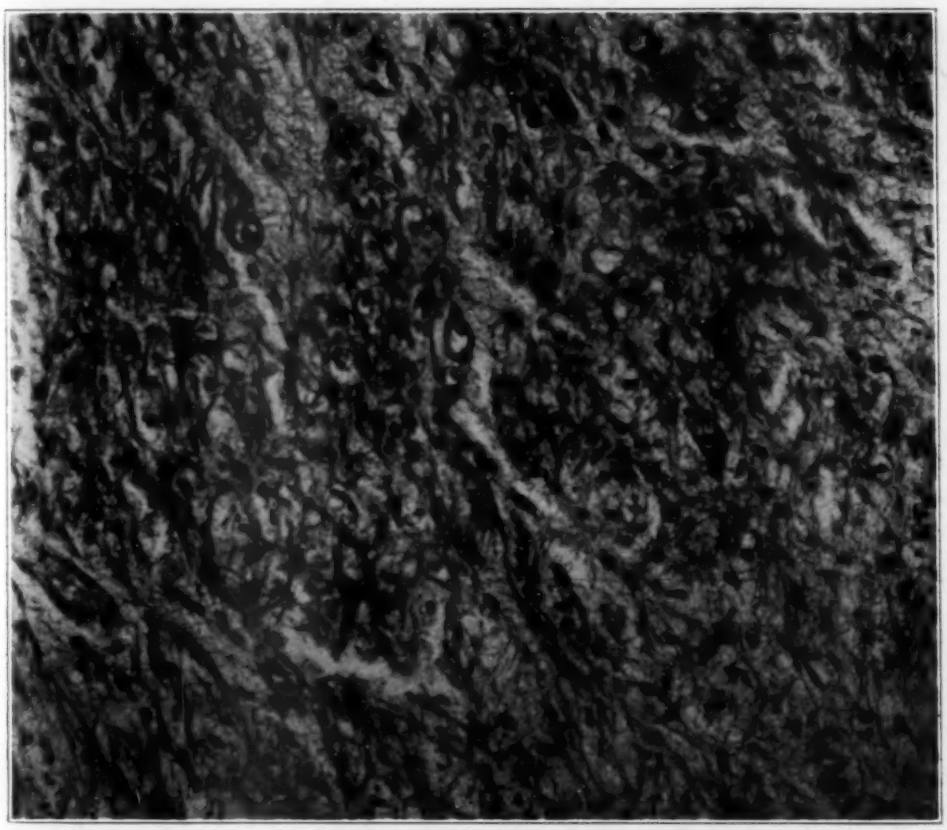

Fig. 3 (case 1).—Low power photomicrograph of a section of the leiomyoma shown in figure 1. Note the poorly matured leiomyoblasts.

The diagnosis was leiomyoma of the gastric wall.

Photomicrographs are shown in figures 3 and 4. From a clinical point of view the lesion has been considered a benign tumor of the stomach, as it was well encapsulated and without evidence of infiltration and as there was no regional glandular enlargement. The liver appeared normal at operation, and save for a few adhesions around the duodenum the abdomen presented no other abnormalities.

The patient had an uneventful convalescence and was reported to be well nineteen months after operation.

CASE 2.[2]—An Italian cook, aged 44, was admitted to the New York Hospital with the complaint of epigastric pain of five years' duration. This pain occurred characteristically from fifteen to thirty minutes after meals and lasted from forty-five minutes to one hour. It was relieved by taking sodium bicarbonate or by assuming a recumbent position. Two months before admission the patient vomited frequently after eating. Anorexia developed, and there was a loss of weight of 20 pounds (9.1 Kg.) in the six weeks prior to the patient's admission to the hospital. Dietary measures failed to give relief from the symptoms. There was no melena and no hematemesis.

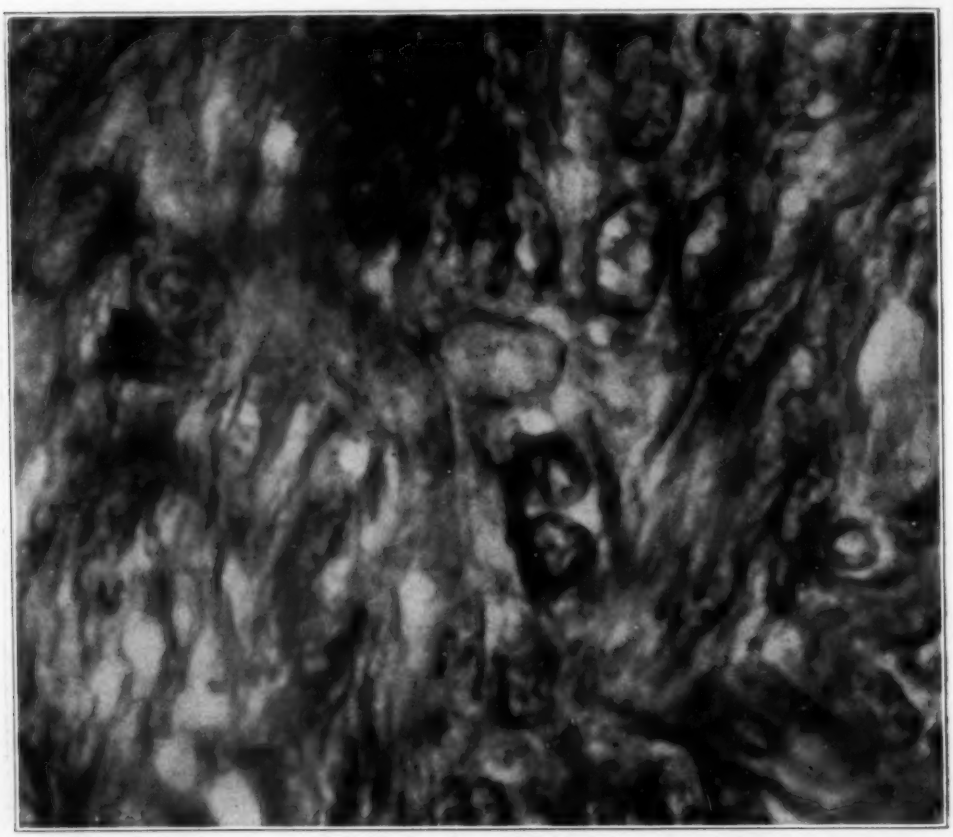

Fig. 4 (case 1).—High power photomicrograph of a section of the leiomyoma shown in figure 1. Note the large, ovoid and somewhat hyperchromatic nuclei surrounded by poorly consolidated muscle substance.

The family history was irrelevant, and the past history was not remarkable. At the age of 9 years the patient had an operation for the removal of a right inguinal gland.

He had occasional nocturia, but urinalysis gave negative results.

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2. Dr. Charles L. Gibson kindly gave me permission to include this case report.

Physical examination showed that the man evidently had lost some weight; he appeared chronically ill. The only significant finding was an elongated epigastric mass which was somewhat tender on palpation and which could not be sufficiently well outlined for measurement. The blood pressure was 120 systolic and 80 diastolic.

The laboratory tests resulted in the following findings: red blood cells, 4,500,000; white blood cells, 11,600, and hemoglobin, 90 per cent. The differential count showed 72 per cent polymorphonuclears, 5 per cent monocytes and 1 per cent eosinophils. The Wassermann reaction of the blood was negative, and the stool showed no blood. Analysis of the gastric contents after an Ewald test meal showed 27.6 units of free hydrochloric and 59.8 units of total acid. The blood urea content was 18 mg. per hundred cubic centimeters, and the icteric index, 7.

A roentgenogram of the gastro-intestinal tract showed a persistent filling defect in the antrum involving both curvatures. Six hours after a barium sulfate meal there was no sign of gastric retention.

The operation, performed by Dr. Gibson, revealed a movable tumor the size of "a silver dollar" in the prepyloric region. It was described as a hard irregular grayish tumor. There was no glandular enlargement. A Polya-Mayo resection of the lower one third of the stomach was carried out.

Dr. Lawrence Smith, who made the pathologic examination of the tumor, described it as follows: The specimen consisted of the terminal 3 inches (7.6 cm.) of the stomach and approximately 1 inch (2.5 cm.) of duodenum. There was definite thickening of the pyloric ring, which was most marked on the side of the lesser curvature. Here a disklike mass, approximately 1.5 cm. in diameter, could be felt beneath the mucosa but adherent to it centrally. Its lower margins appeared to be free; centrally it merged with a small sausage-shaped semifluctuant tumor, 2.5 by 1 cm. in diameter. On section it appeared to be composed of irregularly arranged strands of hypertrophied muscle tissue. The deeper discoid mass was extremely dense in consistence and obviously fibrosed. The mucosa showed no erosions, and its adherence to the mass was probably secondary to inflammatory changes.

A frozen section of the larger mass confirmed the impression given by the gross specimen that it was a simple benign tumor of smooth muscle origin. The disklike tumor was composed of dense connective tissue which showed some myxomatous degeneration. There was no definite evidence of malignancy after careful study. There were many large pale-staining clear cells reminiscent of signet ring cells. They, however, appeared to resolve themselves into fat cells or large mononuclear phagocytes laden with lipoids. A photomicrograph of a section is shown in figure 5. The general reaction was characterized by fibrosis and chronic inflammatory cellular infiltration. Superficial ulceration and repair were noted in small areas of the mucosa.

The diagnosis was gastric ulcer (healed) and leiomyoma of the wall of the stomach.

The patient made an uneventful recovery and was discharged on the twentieth day after operation. Up to the present time attempts to obtain information regarding the late results in this case have been unsuccessful.

CASES OF LEIOMYOMA DISCOVERED AT AUTOPSY

The records of the 33 cases in which a leiomyoma of the stomach was discovered at autopsy have been studied in regard to the rôle played by the tumor in causing death. In only 21 of these cases was the cause of death recorded.

In 6 cases it was clearly stated that death was due to massive gastric hemorrhage. These are the cases of Niemeyer, Kemke, Miodowski, Fischer-Loewenstein, Morgan and Farr and Glenn. In only 4 cases was the size of the tumor mentioned; in 1 it was 4.5 by 5 cm., in 1 1½ by 2 inches (3.7 by 5 cm.), in 1 the "size of an apple" and in 1 the "size of an egg." One tumor was located at the lesser curvature, 1 in the middle of the greater curvature, 1 at the fundus and 1 on the anterior gastric wall. The ages of the patients ranged from 49 to 70

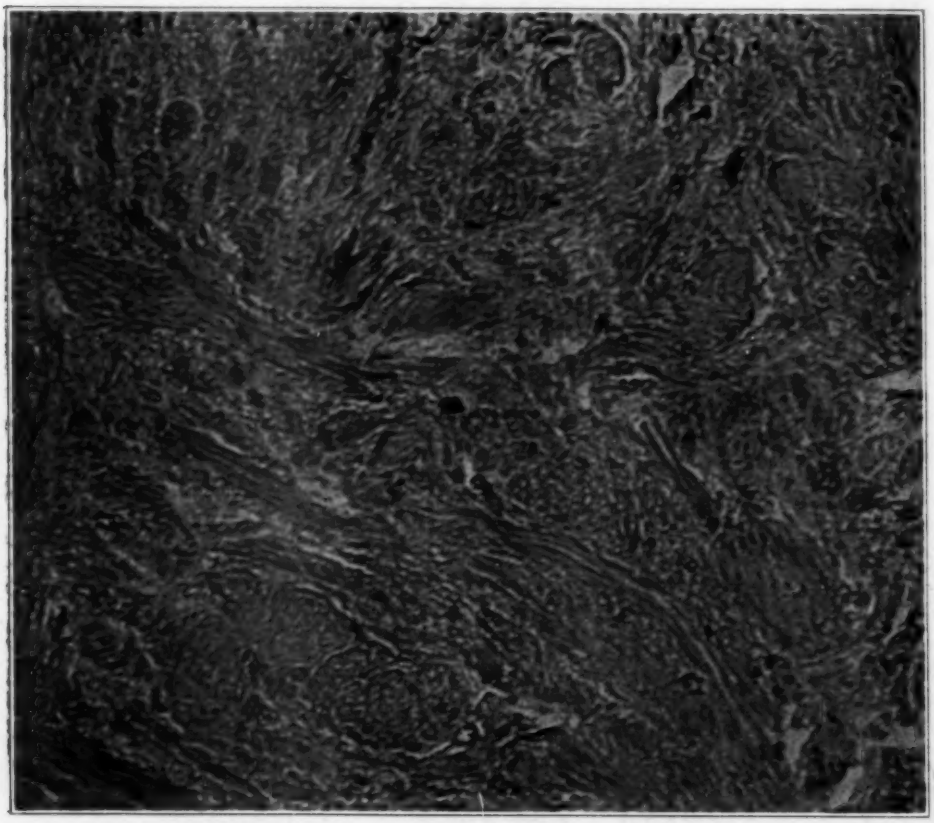

Fig. 5 (case 2).—Low power photomicrograph of a section of a leiomyoma showing the smooth muscle cells.

years. It is significant that in the cases in which the size and location are given, the tumor was described as small and not near the pylorus. These cases aline themselves with those of the group in which the tumor was discovered at operation performed for gastric hemorrhage.

In 13 cases it is clearly stated that the patient died of a cause unrelated to the gastric tumor. These are the cases of Vogel, Virchow, Jean, Cutler, F. Cohen (2 cases), Caminiti, and Mouriquand and

Gardère, Lotsch, Hake (3 cases) and Max. These cases, then, are instances of a type of asymptomatic leiomyoma of the stomach which is discovered incidentally at postmortem examination. In all of these cases the tumor was small and variously described as the size of a nut, pea, cherry, etc. The largest lesion occurred in one of Hake's cases, in which a tumor 8.7 by 5 cm. was found near the cardia. Its location in the stomach may have accounted for the fact that it did not produce any symptoms. The type of case in this group is undoubtedly responsible for the common teaching that a benign tumor of the stomach is of no clinical significance and should be regarded only as a matter of curiosity at autopsy.

One patient (Battey) is said to have died as a result of toxic absorption from the tumor, an hour glass, pedunculated mass, which had enlarged both under the mucosa and under the serosa of the stomach. Several sinuses in its surface discharged foul pus.

In 1 other case, the last of the 20 in which the cause of death was stated, the tumor may have been a contributory lethal factor. In this case (Ferguson) the patient exhibited marked anemia, pellagra and bilateral pleural effusion. The cause of death is not clearly stated in the report, but since the tumor was described as of "unusual size" and at the cardia, it is possible that it was responsible for the chain of clinical events which led to death.

In none of the cases in which the growth was found at autopsy has pyloric obstruction due to leiomyoma been given as the cause of death. The reason for this may be that the symptoms of pyloric obstruction, if at all severe, demand surgical intervention, and the patients undoubtedly have been subjected to operation.

The age of the patient at the time of death was recorded in 19 of the 33 cases as follows:

Age	No. of Cases
10-20	1
20-30	1
30-40	0
40-50	4
50-60	5
60-70	4
70-80	1
80-90	3

Of the 21 cases in which the sex was recorded, 9 were in males and 12 in females. The race was mentioned in only 3 cases; all the patients were Caucasians.

The position of the gastric tumor is reported in only 19 cases. In none of these was it obstructing the pylorus, but in 3 (Jean, F. Cohen and Caminiti) the position of the tumor was recorded as near or

"around" the pylorus. The cause of death in these 3 cases was: (1) lobar pneumonia, (2) death following operation for myoma of the uterus and (3) pulmonary tuberculosis. The location of the tumor in the stomach was as follows in the 19 cases in which it was noted:

Location	No. of Cases
Posterior wall	1
Lesser curvature near cardia	4
Anterior wall near pylorus	2
Lesser curvature	1
Greater curvature	2
Fundus	2
Around the pylorus	1
Near the pylorus	1
Middle of the greater curvature	1
Posterior surface	1
Posterior wall near the cardia	1
Cardia	1
Between the greater and the lesser curvature	1

In only 24 of the 33 cases was reference made to the size of the tumor. The largest was 9 by 8 cm. Many were listed as the "size of a nut," "bean," etc. In 1 case there were 4 pea-sized tumors in the stomach (Laboulbène) and in another, multiple leiomyomas, 60 in all, of the gastro-intestinal tract, only 1 of which was in the stomach (Nazzarri).

The weight of the leiomyoma discovered at autopsy was given in only 2 cases; in Morgagni's case the tumor weighed 1 pound (0.5 Kg.); this was the first leiomyoma of the stomach to be reported (1762). In Perls-Neelsen's case the tumor weighed 6 Kg. This tumor has often been referred to (Thompson) as the heaviest leiomyoma of the stomach ever reported, but the weight has been mentioned in so few instances that it is impossible to accord special significance to the tumor reported by Perls-Neelsen.

In only 6 of the 33 cases of leiomyoma of the stomach found at autopsy were symptoms recorded. In these 6 cases death was due to gastric bleeding, and the symptoms were tarry stools and massive hemorrhage from the stomach. The 33 cases in which leiomyoma of the stomach was discovered at autopsy were the cases of Morgagni, Foerster, Vogel, Virchow, Jean, Cutler, Laboulbène, Perls-Neelsen, Niemeyer, Kemke, Steiner (3 cases), F. Cohen (3 cases), Nazzarri, Borst, H. Cohn, Caminiti, Miodowski, Fischer-Loewenstein, Max, Battey, Mouriquand and Gardère, Anitschkow, Lotsch, Hake (3 cases), Ferguson, Farr and Glenn and Morgan.

COMMENT

A review of the literature on benign tumors of the stomach of muscle cell origin reveals the following facts in regard to the incidence and pathologic characteristics of gastric leiomyomas:

The distribution in regard to sex is practically equal.

The youngest patient in whom such a tumor is known to have occurred was 9 years old.

Such a tumor may occur not only in the stomach but also in the esophagus and intestines and may be multiple in all of these organs.

The tumor may be found in any portion of the stomach.

Gross pathologic descriptions, in general, establish the fact that this type of tumor is encapsulated and nodular and that on section the surface bulges. The tumor may be external and project into the peritoneal cavity, in which case the serosa of the stomach is freely movable over the capsule; it may be internal and invade the lumen of the stomach, in which case the mucosa is freely movable over its capsule (Steiner). Definite mucosal folds or crypts have been described in the mucosa of the stomach over the surface of the tumor, and in a few cases small ulcerations of the mucosa have been reported. The weights of the tumors vary exceedingly; the heaviest tumor weighed 6 Kg. The variation in size is equally marked. The smallest tumors are described as "pea-sized," while the largest have been reported to be "as large as a man's head."

SUMMARY

A careful study of the literature on benign tumor of the stomach has been made for the purpose of collecting all reported cases of true gastric leiomyoma and of correlating, as far as possible, the clinical and pathologic pictures. Reports of 56 cases were found in the literature, and 2 new cases are added. Twenty-five of these were found at operation and 33 at autopsy.

An analysis of the clinical and pathologic picture in the 56 cases suggests their classification under four headings, as instances of:

(*a*) Small leiomyoma which occurs near the pylorus and produces pyloric obstruction.

(*b*) Large leiomyoma which occurs in the fundus of the stomach and causes partial gastric obstruction.

(*c*) Small leiomyoma located at a distance from the pylorus which gives rise to severe gastric hemorrhage.

(*d*) Small leiomyoma which is asymptomatic.

Two new cases are described in detail; 1 in which gastric hemorrhage made operation imperative and 1 in which a small tumor at the pylorus caused obstruction, which was relieved by resection of the tumor.

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HYPOPARATHYROIDISM FOLLOWING OPERATION FOR HYPERPARATHYROIDISM DUE TO ADENOMA TOLERANCE FOR PARATHYROID EXTRACT

ROY D. McCLURE, M.D.
DETROIT

Death following the surgical removal of a parathyroid tumor or following the accidental removal of the parathyroid glands in the course of a thyroidectomy is sufficiently rare to justify the report of such a case and a discussion of the probable causes of death following removal of a parathyroid adenoma when the use of calcium salts, vitamin D and parathyroid extract and transplantation of parathyroid tissue failed.

Aub [1] was the first to report and analyze the failure of parathyroid extract to control parathyroid tetany after thyroidectomy.

The patient at the age of 18 underwent a subtotal thyroidectomy twice within the year 1917 for symptoms of exophthalmic goiter of three years' duration. Two months after the second operation, attacks of choking and carpopedal spasm with edema of the face and extremities developed. Two years after the second thyroidectomy, operation was necessary for bilateral cataract. Parathyroid extract was first given in 1926, nine years after thyroidectomy. At that time the patient was still having attacks of tetany; the basal metabolic rate was minus 18 per cent (before thyroidectomy it had been plus 45 per cent); the serum calcium content was 4.3 mg. per hundred cubic centimeters, and the inorganic phosphorus content, 5.6 mg. Fifteen units of parathyroid extract given daily for a week, together with thyroid extract, raised the serum calcium content to 6 mg. and the basal metabolic rate to plus 11 per cent, the blood phosphorus content falling to 4.2 mg. As a result, the attacks of tetany ceased. The administration of parathyroid

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From the Henry Ford Hospital.

Dr. Arthur B. McGraw and Dr. Don C. Robertson have helped in the preparation of this paper.

Read before the Section on Surgery, General and Abdominal, at the Eighty-Seventh Annual Session of the American Medical Association, Kansas City, Mo., May 14, 1936.

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extract, however, had to be continued and gradually increased in order to prove effective. Finally, after some months, doses of 100 units had no effect. The eventual results of this failure were disastrous, for the persisting low serum calcium content was accompanied by severe attacks of tetany, associated with bronchial and pharyngeal spasm and unconsciousness, and in such an attack the patient died.

Aub [1c] interpreted this phenomenon as an "immunity" to parathyroid extract. When such an immunity appears, even large doses of parathyroid extract exert no influence on the calcium or phosphorus content of the blood. He stated that this loss of potency has lasted in one case for a year and is dependent on resistance to the preparation and not on drainage of the storehouse of calcium, for an increase in the excretion of calcium followed the administration of ammonium chloride after parathyroid extract had proved ineffective.

The first fatal case of hypoparathyroidism following parathyroidectomy in this country was reported by Wilder, Camp, Robertson and Adams.[2]

The patient, a woman aged 48, had had some alleged rheumatic symptoms consisting of pain in the knees and the lower part of the back radiating down the thighs for three years. The severity of the pain confined her to bed. In spite of roentgen evidence of osseous rarefaction, a diagnosis of hyperparathyroidism was rejected on account of a normal content of serum calcium and serum phosphorus.

Therapy with viosterol and calcium lactate caused a remission of symptoms for nearly two years, when the symptoms again became serious and further roentgenograms showed increased rarefaction of the pelvic bones, with features clearly characteristic of fibrous osteitis. The calcium and the phosphorus content of the serum were again within normal limits, but the phosphatase content of the blood was abnormally elevated, and there was a slightly negative calcium and a positive phosphorus balance when the patient was on a diet containing only 0.159 Gm. of calcium. Surgical exploration at this time by Dr. F. W. Rankin revealed a parathyroid tumor 2 by 1.5 by 1 cm. in the groove between the trachea and the esophagus. On section, the structure was that of an adenoma.

After operation the serum calcium content rapidly fell to 5.5 mg. per hundred cubic centimeters. The patient manifested symptoms of tetany, which were not relieved by large daily doses of dibasic calcium phosphate ($CaHPO_4$). The tetany yielded to an injection of 15 units of parathyroid extract and was subsequently prevented by the daily administration of 20 Gm. of calcium lactate. The pain completely disappeared, and for a short time there was a positive calcium balance. At the end of the third week, however, a negative calcium balance again set in, accompanied by nausea, vomiting, meteorism, abdominal cramps and diarrhea. The calcium and the phosphorus content of the serum fell below normal levels and did not yield to injections of parathyroid extract. Nutritional edema developed, and the patient died one and one-half months after operation.

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The following case has many features similar to the one just reported, even to the resistance of the patient to parathyroid extract, for which my colleagues and I have attempted to find an explanation.

E. D., a white woman aged 51, married, was admitted to the Henry Ford Hospital on March 1, 1934. Her chief complaint was soreness of the left leg (at the site of fracture thirty-one months before) and a hard, painless swelling below the right elbow. She had typhoid at the age of 17, arthritis in all the joints for the past seven years, pneumonia and pleurisy five years before admission, occasional nocturnal dyspnea and frequency and urgency of urination.

The present illness began six years before admission, when a fall on the right arm resulted in a hard painless enlargement just below the right elbow, which had persisted. Two and one-half years before admission the patient slipped on

Fig. 1.—Roentgenogram of the left femur, showing a fracture in the upper third of the shaft. Note the osteoporosis and thinning of the cortex. The picture was taken at the Providence Hospital on Sept. 2, 1931.

a waxed floor and fractured the shaft of the left femur (fig. 1). She was hospitalized elsewhere for six weeks and then returned home after a cast was applied. When allowed on crutches three months after the accident, she noted soreness and tenderness at the site of the fracture, which never disappeared. She has never been able to bear much weight on the left leg and has noticed local heat at the site of injury from time to time.

Physical examination revealed the following: temperature, 98.2 F.; pulse rate, 76; respiratory rate, 18, and weight, 127 pounds (57.6 Kg.). The patient appeared tired and worn. There was some graying of the hair, but it was normal in texture and distribution. The thyroid gland was not enlarged and felt smooth. A marked pulsation, synchronous with the heart beat, was palpable in the suprasternal notch and above the right clavicle. The heart sounds were a little distant

but regular, and no murmurs were audible. The blood pressure was 140 systolic and 84 diastolic. There was slight tenderness over the descending colon. Some leukoplakia of the vulva was noted. There was roughly 2.5 cm. of shortening of the left lower extremity, with a painful tender fusiform enlargement near the midportion of the femur. A hard bony fusiform enlargement of the right ulna just below the elbow was noted. There was a hallux valgus deformity on the right.

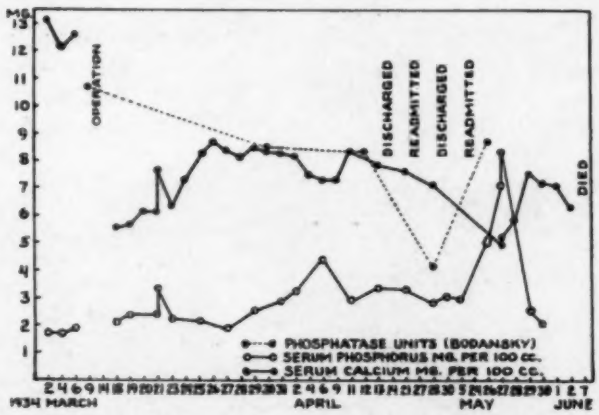

Fig. 2.—Curves showing the values for calcium, phosphorus and phosphatase.

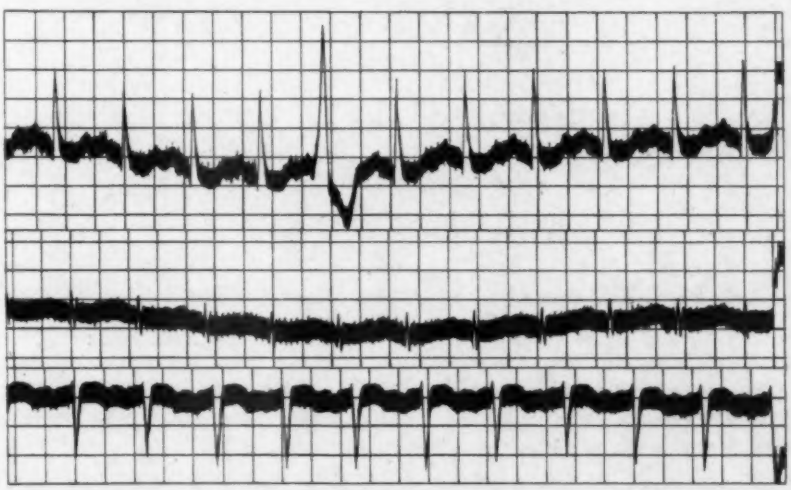

Fig. 3.—Electrocardiogram made before resection of the parathyroid adenoma. The RT time was 0.2 second (normal RT time, 0.26 to 0.28 second). The record was taken on March 5, 1934.

One determination of the basal metabolic rate was minus 3 per cent. Urinalysis gave negative results. The hemoglobin content was 83 per cent, or 13.2 Gm., and the leukocytes numbered 7,300. The Wassermann test was negative. The calcium content of the blood was 12.2 mg. and the phosphorus content, 1.8 mg. per hundred

cubic centimeters (fig. 2). There was 10.72 units (Bodansky [3]) of phosphatase. The calcium balance averaged plus 0.31 Gm. per day for one three day period of study.

The electrocardiogram showed a diphasic T wave in leads I and II, slight left ventricular preponderance, occasional ventricular extrasystoles and sinus tachycardia and indicated some degree of myocardial degeneration. There was a slight shortening of the RT time to around 0.2 second (fig. 3). This corresponds with the electrocardiographic changes previously observed by Spalding [4] in cases of hyperparathyroidism.

The roentgenograms (fig. 4) of the skull, left femur, pelvis, left humerus, right forearm and mandible showed osteoporosis varying from a moderate to a marked amount. Cystlike areas were present in the mandible, the right ulna and the left femur. The latter also showed an old fracture at the junction of the

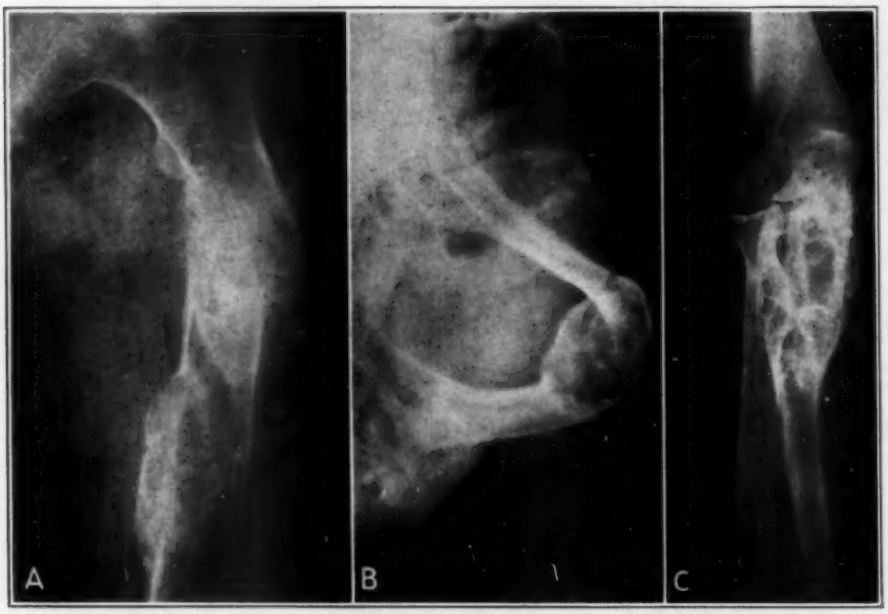

Fig. 4.—*A*, roentgenogram of the left femur before operation, taken on March 1, 1934, at the time of the patient's admission. *B*, roentgenogram of the mandible before operation, taken on March 6, 1934. *C*, roentgenogram of the right radius and ulna before operation, taken on March 5, 1934. Several small cystlike areas were also present in the lower ends of these bones.

middle and the upper third, where an extensive cystlike process was present. Roentgenograms (fig. 1) of the site of the fracture received three years before revealed a marked amount of osteoporosis and some thinning of the cortex in addition to the displaced fragments. The foregoing changes were felt to be quite characteristic of osteitis fibrosa systica secondary to hyperparathyroidism.

3. All phosphatase determinations in this report are expressed in terms of Bodansky units.

4. Spalding, E. D., quoted by Ballin, M.: Parathyroidism, Ann. Surg. **96**: 649-665, 1932.

Resection of the parathyroid adenoma and partial thyroidectomy were performed on March 14.

The thyroid gland was well exposed on each side of the neck, through the conventional collar incision with retraction of the ribbon muscles. The gland was slightly enlarged, and there was a firm nodule 2 cm. in diameter lying within the lower pole of the right lobe (fig. 5). Careful search was made for the parathyroid glands in the usual position, but none was identified. The right lobe of the thyroid was removed in order to make sure, if possible, that the parathyroid glands were removed, as it was thought that the tumor completely embeded in the thyroid was not composed of parathyroid tissue. Immediately on removal of the thyroid tissue it was sectioned by the pathologist. (See his note.) Search of the left lobe of the thyroid failed to show any parathyroid adenoma, and a portion

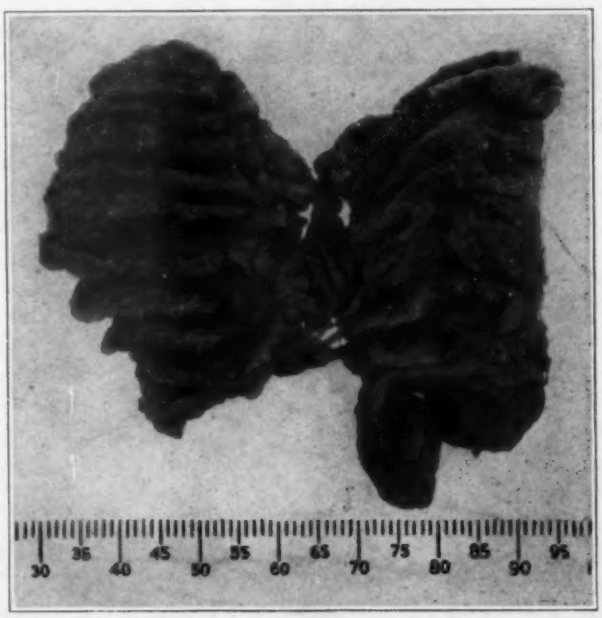

Fig. 5.—Photograph of a dissected gland, showing parathyroid adenoma embedded in thyroid tissue of the right lower pole. The adenoma measured 2 cm. in diameter and presented a thick fibrous capsule and a cystic central portion containing brown fluid.

of the lower pole of this lobe was removed. Careful search, however, of the tissue removed failed to show any parathyroid tissue present, excepting the tumor enclosed in the lower pole of the right lobe.

The following is the pathologic report by Dr. Frank Hartman: Section through the lower pole of the right lobe revealed a cystic adenoma (fig. 5) 2 cm. in diameter. The outer portions of the adenoma were yellowish brown and solid. From this tissue finger-like processes extended into the cyst, which was filled with bloody fluid. The tissue was soft and friable. In addition to the tissues mentioned there were a number of small bits of tissue which had been removed during the course of examination from the surface of the thyroid gland and

examined by frozen sections. These pieces of tissue were shown histologically to be isolated lobules of thyroid tissue, lymphoid tissue and fatty tissue. Frozen sections unfortunately were not made of the adenoma, and in the gross specimen this was interpreted as a degenerating adenoma of the thyroid gland largely because of its location in the substance of the gland.

Microscopic examination of sections from different portions of thyroid tissue showed the acini of the gland to be rather small and lined by flattened epithelium.

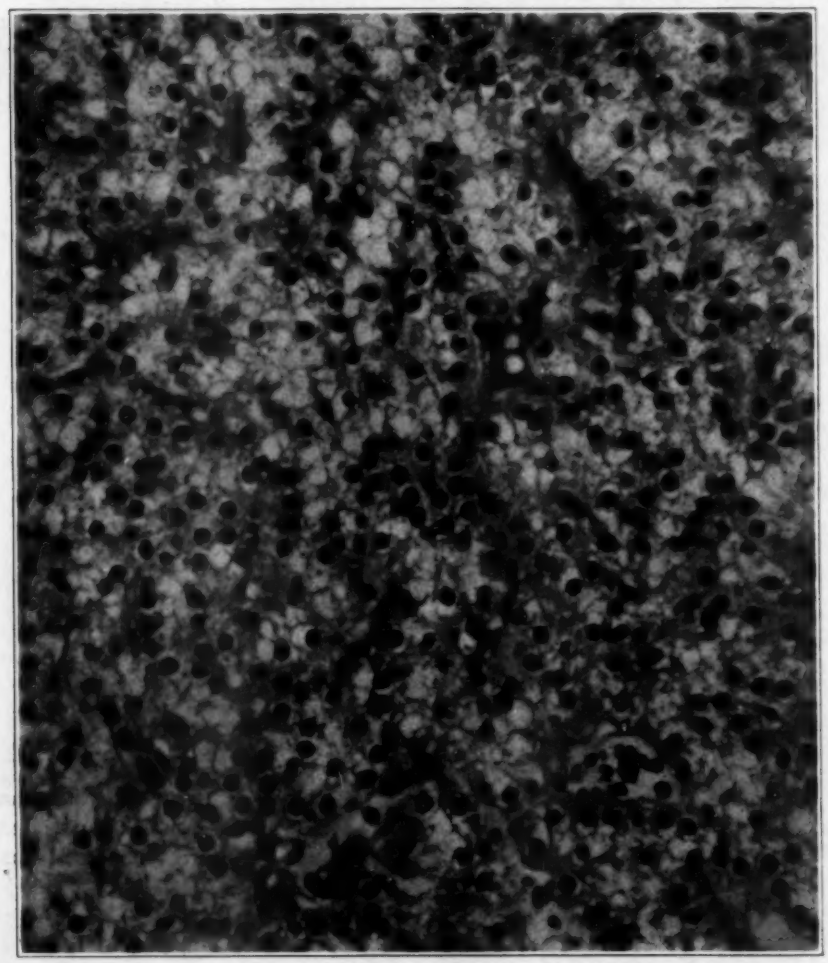

Fig. 6.—Medium power photomicrograph showing a group of oxyphilic cells at the periphery of the tumor. Some cells have a larger clear space about the nucleus.

The lumens were filled with dense pink-staining colloid material. Here and there collections of small round cells were seen.

Sections from the tumor (figs. 6 and 7) in the lower pole of the right lobe of the thyroid gland showed the same, surrounded by a rather dense fibrous capsule.

Within the capsule there was a rather thick layer of large polyhedral cells, which for the most part had pink-staining cytoplasm: The nuclei were relatively large and hyperchromatic. There was a clear space about the nucleus in most of the cells, even in this area. As the central portions of the tumor were approached, the vacuolation was more pronounced, and in some areas the cytoplasm was almost entirely clear. In the latter areas the nucleus tended

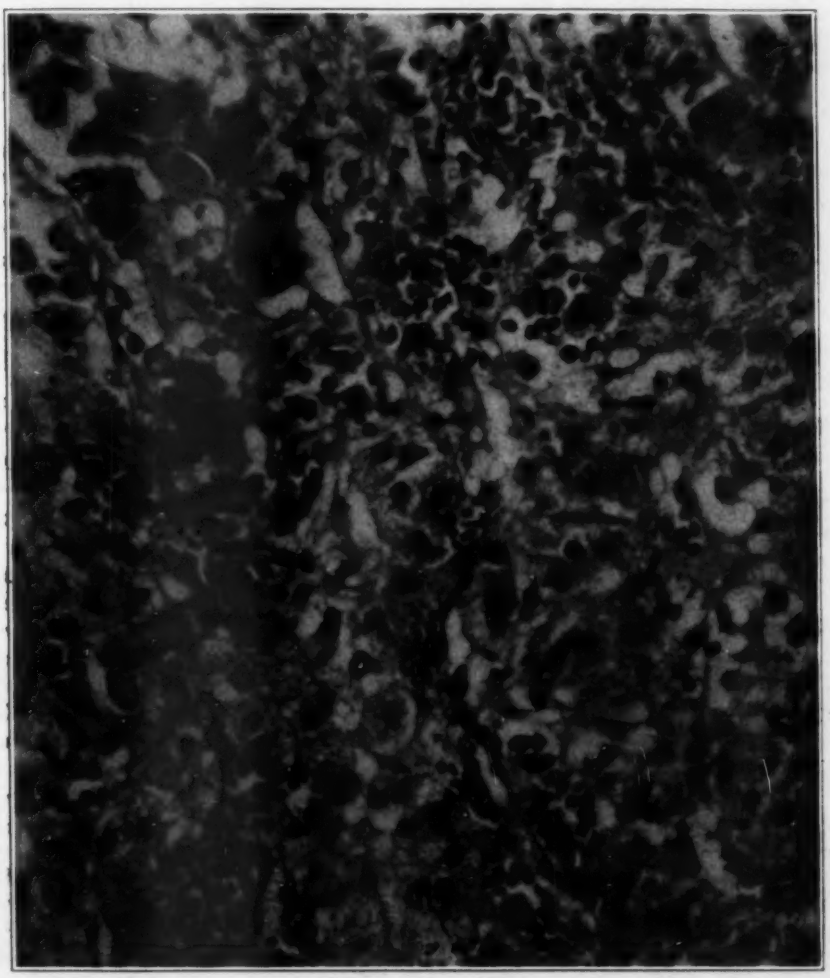

Fig. 7.—High power photomicrograph showing more detail of the individual cells in figure 6.

to lie near one end of the cell. The predominant cell then was a vacuolated oxyphil cell, or, as Castleman and Mallory designated it, a "transition *wasserhelle*." These cells were arranged in irregular tubules and in small alveoli in some places, and also, even in the most solid portions, there were small cysts. The central portions of the tumor were almost entirely cystic, with finger-like processes of the

cells extending throughout the cystic areas. There was little stroma throughout the tumor, and the most solid portions were quite vascular, large dilated blood spaces being seen between the tubules. It seems that this parathyroid adenoma should be designated as a transition *wasserhelle* cell type.[5]

A diagnosis was made of cystic degeneration and hemorrhagic adenoma in the lower pole of the right lobe of the thyroid gland. The thyroid gland was normal.

Immediately after operation, auricular fibrillation developed. Digitalis was given, and regular rhythm was restored within eight hours. The following morning the patient felt better than she had for a year. Pains previously complained of in the back and legs had entirely disappeared, and she could lift her feet from the bed without pain for the first time in months. Four days after operation, however, she complained of a peculiar sensation in her hands, but no definite carpopedal spasm was present. Chvostek's sign was positive, but Trousseau's sign was negative. Ten cubic centimeters of calcium gluconate was given intravenously. Carpopedal spasm developed the same night, and the patient complained of a "dead feeling" over the entire body. This again was relieved by 10 cc. of calcium gluconate. Mild attacks of tetany continued for the next three days, at which time treatment was started with calcium lactate, viosterol, calcium gluconate and parathyroid extract. She improved rapidly and was discharged on April 14, one month after operation.

At home she received 20 grains (1.3 Gm.) of calcium lactate three times a day, 10 drops of viosterol (containing 10,000 U. S. P. XI units of vitamin D per gram) three times a day and 1 cc. (20 units) of parathyroid extract each day. The serum calcium content showed a tendency to fall unless parathyroid extract was administered daily.

The results of determinations of calcium, phosphorus and phosphatase during observation are tabulated and graphically represented (fig. 2).

On April 27, seventeen days after discharge, the patient reentered the hospital for three days of observation and treatment. She complained of nausea and felt nervous and shaky. Chvostek's sign was positive. Calcium gluconate administered intravenously gave relief. Studies of the blood the day after admission showed 7.2 mg. of calcium, and 2.86 mg. of blood phosphorus per hundred cubic centimeters of blood and 4.18 units of phosphatase. The patient was discharged on April 30 feeling much improved. She was again placed on a regimen of viosterol, calcium lactate and parathyroid extract.

On June 24 she again reentered the hospital, with the history of having vomited for two weeks and of having paroxysms of choking and dyspnea. She had been

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5. Castleman and Mallory (The Pathology of the Parathyroid Gland in Hyperparathyroidism, Am. J. Path. **11**:1-72, 1935) stated: "The neoplasias of the glands serve to reinforce the arguments against generically different cell types and favor the concept of a fundamental cell from which all others are derived. Pure tumors of either the oxyphil or wasserhelle type unaccompanied by any chief cell forms were not present in our series, and we find the occasional reports in the literature unconvincing. When cells of either of these specialized types are predominant numerous transition forms of the chief cell can always be demonstrated. The chief cell in other words is the only invariable component of a tumor, obviously the basic fundamental cell and possibly the only proliferative form. The other cell types derived from it are to be regarded as degrees of differentiation or as involution forms."

under the care of her family physician during the interval. Carpopedal spasm had repeatedly been present, and she was so weak that she was unable to leave her bed. She had kept nothing down that was taken by mouth for three days, and for the past thirty-six hours she had been having frequent paroxysms of dyspnea, during which time she could hardly get her breath. At these times she choked and had a feeling of the presence of phlegm in her throat that she was unable to raise.

On examination, she appeared drowsy and mentally sluggish, although she was conscious and perfectly rational. The pulse was weak but regular, and there was a slight tachycardia. There was evidence of moderate dehydration. Chvostek's sign was strongly positive; but Trousseau's was negative. She was able to retain little that was given by mouth.

During the first night of her admission she became very cold and clammy, and it was impossible to detect her pulse. No true tetany was observed; but 10 cc. of calcium gluconate was given intravenously. No appreciable effect was noted. The pulse remained of poor quality during the remainder of the night and the following day. On the second day of her admission the serum calcium content was 5 mg. and the phosphorus content 5.27 mg. per hundred cubic centimeters; there was 8.73 units of phosphatase. The patient was having repeated small emeses. Her body was cold and clammy, yet subjectively she felt warm. The pulse remained feeble, and the blood pressure was unobtainable most of the time in spite of the parenteral administration of fluids and calcium gluconate intravenously. The third day she was given 20 units of parathyroid extract, with some temporary improvement. Two parathyroid glands which had just been removed during the course of thyroidectomy on another patient were implanted in the rectus muscle, as first suggested by Halsted.[6]

As the patient was retaining nothing by mouth, the problem of vitamin D intake presented itself. This was attempted by administering it intramuscularly, by rectum and intranasally by means of a nasal spray. The amounts and frequency of the administration of parathyroid extract and calcium gluconate were increased, but apparently without effect, as she continued to have longer and more frequent periods of circulatory collapse. Generalized edema developed, which was felt to be on a nutritional and possibly thyroid deficiency basis. Four days before death therapy with thyroid extract and digalen was begun, which apparently had no effect, as the patient became rapidly worse, death occurring on the thirteenth day of admission, approximately four months after the original operation. The calcium content remained persistently low, while the phosphorus content rose to a high level of 7.2 mg., yet no tetany occurred.

The following conditions were discovered at autopsy: osteitis fibrosa cystica, hemorrhagic diathesis, bilateral hydrohemothorax, atelectasis of the lower lobe of the right lung, calcareous deposits in the renal tubules and total edentia.

In a careful search of the literature I was able to find over one hundred and twenty-five cases of proved hyperparathyroidism in which a parathyroid adenoma was found and removed in whole or in part. Eleven of the patients were dead at the time of the report (nine women

6. Halsted, W. S.: Transplantation of the Parathyroid Glands, Proc. Path. Soc. Philadelphia **11**:109-114, 1908.

and two men). Seven of these [7] exhibited signs of parathyroid tetany, and three eventually died, undoubtedly, from the effects of hypoparathyroidism. Renal complications, no doubt secondary to the effects of hyperparathyroidism, were responsible for four deaths.[8] Unexpected cardiac complications were the cause of two deaths.[9] One patient died a few years after operation from causes not stated,[10] and the remaining patient [11] died suddenly one night from suffocation, seven months after operation.

The case reported from the Henry Ford Hospital has been presented not only on account of the rarity of the condition but on account of the following interesting points:

1. The inclusion of a cystic parathyroid adenoma entirely within the lobe of the thyroid.

2. The demonstration of osteoporosis of the femur at the time of fracture, two and one-half years before the diagnosis of hyperparathyroidism was made. We were fortunate in being able to obtain this roentgenogram from another hospital. In contrast to this osteoporosis, our roentgenograms show a fully developed picture of osteitis fibrosa

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7. (*a*) Beck, A.: Aussprache, Arch. f. klin. Chir. **152**:123-124, 1928. (*b*) Rosedale, R. S.: Fibrocystic Disease of the Bones Associated with Tumor of a Parathyroid Gland, Am. J. Path. **8**:745-751, 1932. (*c*) Albright, F.; Baird, P. C.; Cope, O., and Bloomberg, E.: Studies on the Physiology of the Parathyroid Glands: IV. Renal Complications of Hyperparathyroidism, Am. J. M. Sc. **187**: 49-65, 1934. (*d*) Richardson, E. P.; Aub, J. C., and Bauer, W.: Parathyroidectomy in Osteomalacia, Ann. Surg. **90**:730-741, 1929. (*e*) Hannon, R. R.; Shorr, E.; McClellan, W. S., and DuBois, E. F.: A Case of Osteitis Fibrosa Cystica (Osteomalacia) with Evidence of Hyperactivity of the Parathyroid Bodies; Metabolic Study: I, J. Clin. Investigation **8**:215-227, 1930. (*f*) Bauer, W. K.; Albright, F., and Aub, J. C.: Metabolic Study: II, ibid. **8**:229-248, 1930. (*g*) McClellan, W. S., and Hannon, R. R.: Metabolic Study: III, ibid. **8**:249-258, 1930. (*h*) Albright, F.; Bauer, W.; Claflin, D., and Cockrill, J. R.: Studies in Parathyroid Physiology: Effect of Phosphate Ingestion in Clinical Hyperparathyroidism, ibid. **11**:411-435, 1932. (*i*) Wilder, Camp, Robertson and Adams.[2]

8. Churchill, E. D., and Cope, O.: The Surgical Treatment of Hyperparathyroidism Based on Thirty Cases Confirmed by Operation, Ann. Surg. **104**:9-35, 1936.

9. Babcock, W. W.: Multiple Giant-Celled Tumor of Bone, Osteitis Fibrosa Cystica, Paget's Type of Skull, and Renal Calculi, Apparently Due to Large Deeply Placed Parathyroid Tumor, S. Clin. North America **12**:1387-1392, 1932. Sorensen, Anshelm: Un cas de ostéite fibreuse généralisée traitée par l'enlèvement d'une tumeur parathyroïdienne, Acta chir. Scandinav. **74**:485-490, 1934.

10. Gutman, A. B.; Swenson, P. C., and Parsons, W. B.: The Differential Diagnosis of Hyperparathyroidism, J. A. M. A. **103**:87-94 (July 14) 1934.

11. Eggers, quoted by Mandl, F.: Therapeutischer Versuch bei einem Falle von Ostitis fibrosa generalisata mittels Exstirpation eines Epithelkoerperchentumors, Zentralbl. f. Chir. **53**:260-264, 1926; **56**:1739-1745, 1929.

cystica. Lahey and Haggart [12] have pointed out that osteoporosis may exist as an early stage of the typical osteitis fibrosa cystica of Recklinghausen, as seen in hyperparathyroidism.

3. The development of tolerance or immunity by a patient to parathyroid extract.

4. A possible explanation of the cause of this tolerance to parathyroid extract.

There seems to be little doubt that in the three patients whose histories we have abstracted hypoparathyroidism resulted from the operation, and in two of the patients hyperparathyroidism was changed to hypoparathyroidism. The operation resulted in a disturbance of the calcium-phosphorus metabolism. Parathyroid extract was administered to each of these patients. Its physiologic effect, according to Aub,[13] is (1) to raise the blood calcium and lower the blood phosphorus, (2) possibly to increase the ionized calcium in the blood; (3) to increase the excretion of calcium and phosphorus in the urine, and (4) to obtain the calcium for this increased demand either from a large amount of ingested calcium or from the stores in the bone.

Each of these three patients received immediate benefit from the use of parathyroid extract. Wilder's [2] patient and our patient were given calcium salts and some preparation of vitamin D. After a time each of the patients again became worse and died, though theoretically their deficiency was being replaced. These deaths are apparently due to the gradual loss of the response to parathyroid extract. This failure did not become apparent for several months.

Collip [14] stated that "a state of lowered reactivity, of increased resistance or of actual non-responsiveness may gradually become manifested in those that have been treated for a long period with some glandular extract." He expressed the belief that the inhibitory substance which is found in the blood of animals after prolonged treatment with some hormone extract is a normal constituent of the blood. With prolonged injections of such an extract there would then be an increased production of the respective inhibitory principle. Therefore the danger is present in the use of parathyroid extract of actually adding to the gravity of the condition by causing "an over-production of the inhibitory principle as a result of too persistent treatment."

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12. Lahey, F. H., and Haggart, G. E.: Hyperparathyroidism: Clinical Diagnosis and Operative Technique of Parathyroidectomy, Surg., Gynec. & Obst. **60**: 1033-1051, 1935.

13. Aub, J. S.: Glandular Physiology and Therapy: Parathyroid Hormone Therapy, J. A. M. A. **105**:197-199 (July 20) 1935.

14. Collip, J. B.: Inhibitory Hormones and Principle of Inverse Response, Ann. Int. Med. **8**:10-13, 1934.

Different groups of workers, Katzman, Wade and Doisy,[15] and Du Shane, Levine, Pfeiffer and Witschi,[16] have failed to find any antihormones. Twombly[17] expressed the belief that these substances are protein antibodies for precipitins to the hormone as an antigen can be demonstrated in the immune serums, and hormones inactivated partially by heat or completely by aging seem to be about as efficient in bringing about the formation of these protective substances as active preparations of the hormone. The fact, however, remains that gradually increasing doses of parathyroid extract had to be given in these cases we are reporting and yet with decreasing effect. Moehlig, Murphy and Reynolds[18] have found in their experimental work on dogs that immunity to large doses of parathyroid extract, as measured by the blood calcium, was soon established. Moehlig, in a personal communication, reported a case of hypoparathyroidism in which over $1,200 was spent for parathyroid extract in a year and the patient still required increasing doses. According to Aub,[13] viosterol acts on the body much as parathyroid extract.

Dr. George R. Sharpless,[19] of the laboratory of the Henry Ford Hospital, in a study of the relation of vitamin D and parathyroid extract fed dogs carefully controlled synthetic diets. He has found that:

1. Normal dogs fed either a diet high in calcium and low in phosphorus or a diet with a normal calcium-phosphorus ratio have extensive deposits of calcium in the soft tissues when given viosterol and parathyroid extract but do not have deposits of calcium in the soft tissues when given parathyroid extract alone.

2. Normal dogs acquire a tolerance (immunity?) to parathyroid extract only when in a state of avitaminosis D and do not acquire a tolerance to parathyroid extract when vitamin D is supplied.

3. It is indicated that parathyroid extract may be impotent in the absence of vitamin D.

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15. Katzman, P. A.; Wade, N. J., and Doisy, E. A.: Concerning the Production of Anterior Pituitary Inhibitory Substances, J. Biol. Chem. **56**:lvi-lvii, 1936.

16. Du Shane, G. P.; Levine, W. T.; Pfeiffer, C. A., and Witschi, E.: Experimental "Constant Oestrus" and the Notion of Anti-Gonadotropic Hormones, Proc. Soc. Exper. Biol. & Med. **33**: 339-345, 1935.

17. Twombly, G. H.: Studies of the Nature of Antigonadotropic Substances, Endocrinology **20**:311-317, 1936.

18. Moehlig, R. C.; Murphy, J. M., and Reynolds, L.: Attempt to Produce Paget's Disease by Use of Anterior Pituitary Growth Extract and Parathyroid Extract Calcium Deposits in Kidney and Massive Calcium Deposits in Bone Marrow Produced by These Extracts, Am. J. Roentgenol. **34**:465-474, 1935.

19. Presented before the American Society of Experimental Pathologists, 1935.

COMMENT

In our case, owing to vomiting toward the end of her life, the patient did not receive vitamin D. Just how far the use of ultraviolet rays may have replaced this deficiency we cannot say. In view of Dr. Sharpless' finding in our laboratory, we believe that every effort should be made to promote the use of vitamin D preparations in cases similar to those reported, as his finding is very clear in that a tolerance to parathyroid extract develops in the absence of vitamin D. While vitamin D should be used in the patients with hypoparathyroidism, it might by the same token be advisable to maintain the patient with hyperparathyroidism on a regimen high in calcium and low in vitamin D.

In a recent article, Bower and Mengle [20] reported two deaths from the additive effect of calcium and digitalis given simultaneously. Our patient received these two drugs simultaneously during the last five days of her illness, and it is possible that this may have been a factor in her death, although we are inclined to believe that it was not.

We criticize our operative treatment in that we tried to remove too much parathyroid tissue. Our error was made after examination of frozen sections of bits of tissue from the posterior capsule showed no parathyroid tissue and in our mistaken belief that the cystic nodule within the thyroid was a thyroid adenoma and not a parathyroid tumor.

Churchill [8a] suggested an operation in stages, and we believe that this suggestion deserves careful consideration before any complete excision is done. Indications for such operations on the parathyroid glands may be as clearly worked out as they were for hyperthyroidism, though such operations for hyperthyroidism have become relatively less and less frequent as adequate preoperative preparation with iodine has been used.

It is not known whether the low serum calcium content or the high serum phosphorus content is responsible for the production of tetany, but the present tendency is to believe that the high serum phosphorus content is responsible, and so efforts to reduce this serum phosphorus would seem logical. This can be accomplished temporarily by the intravenous use of dextrose, as shown in the Henry Ford Hospital by Hartman and Foster.[21] Since it is almost impossible to reduce the amount of serum phosphorus by diet alone on account of the wide distribution of phosphorus in foods, recent efforts have been made to

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20. Bower, J. O., and Mengle, H. A. K.: The Additive Effect of Calcium and Digitalis: A Warning, with a Report of Two Deaths, J. A. M. A. **106**:1151-1153 (April 4) 1936.

21. Hartman, F. W., and Foster, D. P.: Clinical Evaluation of Blood Phosphate and Sugar Tolerance Curves: Analysis of Five Hundred Clinical Cases, Am. J. Clin. Path. **2**:289-297, 1932.

do this by mixing aluminum acetate with the foods of dogs and rats.[22] This precipitates the phosphorus as aluminum phosphate, which is not absorbed. Posterior pituitary probably should not be used in the treatment of meteorism in these patients, as it causes a rise in serum phosphorus.

CONCLUSIONS

Postoperative hypoparathyroidism should be a preventable condition.

Stage operations for hyperparathyroidism should be considered (Churchill).

Osteoporosis in hyperparathyroidism is an early stage of osteitis fibrosa cystica.

Parathyroid extract loses its influence when vitamin D is not present. A vitamin D preparation which could be administered either intravenously or subcutaneously would probably be of great value in cases of hypoparathyroidism complicated by extreme nausea and vomiting.

ABSTRACT OF DISCUSSION

DR. FRANK H. LAHEY, Boston: Thanks are due Dr. McClure for his frank discussion of this case, because every one here is going to have to face patients with parathyroid adenoma. There is not any question, if I consider my own experience, that a great many cases of hyperparathyroidism have probably been overlooked in the past years, as proved by the fact that within the last few years they are being found. I have no doubt that there were just as many cases in the past, but physicians did not know how to diagnose the condition. There are certain things about hyperparathyroidism that will accomplish definite results. There must be, I believe, some criteria as to the possible presence of the disease in order that the clinicians may suspect the possibility of this lesion and then turn the patient over to the laboratory workers to demonstrate whether or not it is present. In any patient who has unexplained pain referable to the nerve roots, hyperparathyroidism must be suspected; in any patient who has lost height owing to a round back, due in turn to the softening of the vertebral bodies and angulation at the weight-bearing point in the center of the back, possible hyperparathyroidism must be suspected. In any patient who has spontaneous fractures, demineralization of the bones, Recklinghausen's type of osteitis fibrosa cystica and kidney stones, one must investigate as to possible hyperparathyroidism. If a patient has a low phosphorus or a high calcium content of the blood and a high phosphatase content, it becomes the surgeon's problem. One of the first things a surgeon should have in mind regarding the removal of a parathyroid adenoma is that the adenoma is probably secreting most of the parathyroid extract and for some time after the removal of the adenoma there is likely to be a varying degree of tetany. In most cases in which my colleagues and I have removed a parathyroid adenoma, there has been tetany lasting up to a month; therefore, one must be prepared to handle these patients. If the tetany is too severe, it is difficult to treat. When the patient begins to complain of itching at the end of the nose and tingling in the fingers it is time to begin treatment instead of waiting until

22. Jones, J. H.: The Relation of Serum Phosphate to Parathyroid Tetany, J. Biol. Chem. **114**:liv-lv, 1936.

the condition is too severe to manage. Knowing, then, that the patient with parathyroid adenoma probably will have tetany, the time to undertake the treatment is before it develops. Parathyroid adenomas do not occur in the typical places that used to be described in the textbooks. If they are not found in the usual places, they are in the thyroid or in the mediastinum. It is wise to have a pathologist make frozen sections at the time of exploration, and then good parathyroid glands will not be wasted, and parathyroid glands do not grow on every bush. When they are needed they are needed badly, and unfortunately it is not certain that transplantation is going to work. I think that the physician, particularly the urologist and the orthopedist, must be on the lookout for such tumors, and if this is done more will be discovered. If a parathyroid adenoma is removed, the bones of the patient will recalcify and he will be relieved of his symptoms.

Dr. Brien T. King, Seattle: I have enjoyed Dr. McClure's paper on this subject, having had a similar experience a number of years ago with a patient in whom chronic tetany developed after thyroidectomy for exophthalmic goiter. This patient was fairly satisfactorily relieved of symptoms of tetany during the early stage of the disease by the administration of parathyroid extract, but during the latter months of her illness it was quite ineffective in relieving the muscular spasms. In addition to the usual symptoms of tetany, angina pectoris developed. The attacks of pain always came on synchronously with attacks of tetany. Undoubtedly, the patient had tetany of the cardiac muscle and ultimately died during one of the spasms or cramps and anginal pain. As a result of this experience, I laid down the rule never to remove a parathyroid adenoma or other parathyroid tissue without first having searched for and identified normal parathyroid glands. With the following of this rule, in no case has hypoparathyroidism developed. The most common location for a parathyroid gland is at either superior pole, lying in close contact with the superior thyroid artery near its junction with the pole. If no normal parathyroid tissue is identified, I think that a portion of the adenomatous tissue sufficient to supply the needs of the body should be left in situ. While the subject of hyperparathyroidism is up for discussion, I want to issue a warning that indiscriminate removal of parathyroid tissue for rarefying bone disease will lead to disappointing results in those patients who do not have fairly typical clinical and laboratory findings.

Dr. Roy D. McClure, Detroit: I did not have time to discuss as much as I should like the transplantation of parathyroid tissue which was done in this case. I was fortunate enough to be working in the Hunterian Laboratory when Dr. Halsted was doing his work on transplantation of parathyroid tissue. Halsted's law is that a gland will have a much better chance of "taking" as a transplant if there is a deficiency in that gland in the body. Ours was an ideal case for such a transplantation. Unfortunately, we waited until too late. The transplantation was done only five days before the patient died. The transplant was taken from a patient on whom I was performing a thyroidectomy that day, and we were able to transplant a parathyroid gland immediately. With regard to Dr. Lahey's discussion, I, too, feel that there must be many persons today who have parathyroid tumors that have not been diagnosed. I, personally, have had in the last two years two patients with parathyroid tumors that I operated on. The result in the last patient was simply a miracle, and the rheumatism for which this patient had been treated for a long time was cured. Dr. King is right in opposing operations in all groups of cases in which parathyroidectomy was advocated a few years ago. Not so long ago in Detroit a patient of ours put it up to the judge in the Compensation Court

to decide whether his condition, an ankylosing spondylitis (spondylose rhizomélique or Marie-Strümpell's disease), was due to hyperthyroidism. Following the teaching of Oppel, Ballin and others, we had, in spite of the presence of fairly normal values for serum calcium, phosphorus and phosphatase, performed a subtotal parathyroidectomy on him. After operation the patient was subjectively better; objectively, he was not. In the Compensation Court he claimed compensation from one of the big companies in Detroit. He had been partially strangled by a fellow employee who fought with him while he was detaining this employe for the arrival of the police. From the evidence presented by more or less expert doctors on both sides, the judge in this court decided that the ankylosing spondylitis was due to hyperparathyroidism which had been caused by an injury to the man's neck while he was performing his work.

SPINAL ANESTHESIA

THE EXPERIMENTAL BASIS OF SOME PREVAILING CLINICAL PRACTICES

CoTUI, M.D.
NEW YORK

The purpose of this report is to examine various clinical practices in the use of spinal anesthesia and the assumption concerning them in the light of facts accumulated in a four year study on experimental spinal anesthesia in the dog. The following topics will be discussed: (1) the effect of the narcotic agent on the respiratory center; (2) the use of narcotics as premedication, (3) the effect of a stimulating drug (a 25 per cent solution of pyridine betacarbonic acid di-ethylamide) on paralysis of the respiratory center, produced by procaine hydrochloride, (4) the fall in blood pressure and its cause, effects and treatment, and (5) the use of carbon dioxide as a stimulant.

EFFECT OF THE NARCOTIC AGENT ON THE RESPIRATORY CENTER

In a previous communication,[1] it was shown that if procaine hydrochloride is made to reach the medulla in sufficient strength, either by injection into the cisterna magna or by irrigation of the fourth ventricle, it causes paralysis of the respiratory center. This paralysis was found to be reversible, i. e., with the institution of adequate artificial respiration, spontaneous respiration reestablishes itself in little over an hour. It was further demonstrated that the conclusion of Koster and Kasman,[2] that procaine hydrochloride in a solution of 2.5 per cent applied to the medulla does not cause respiratory paralysis, was based on an error of experimental technic.

Vehrs [3] and recently Thompson,[4] on the ground that large doses of procaine hydrochloride are required to paralyze the respiratory center

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The Ciba Company supplied the pyridine betacarbonic acid di-ethylamide used for this study.

1. CoTui, F. W.: Experimental Studies on Subarachnoid Anesthesia, Surg., Gynec. & Obst. **55**:290-297 (Sept.) 1932.

2. Koster, H., and Kasman, L. P.: Spinal Anesthesia for the Head, Neck and Thorax, Surg., Gynec. & Obst. **49**:617-629 (Nov.) 1929.

3. Vehrs, G.: Heart Beat and Respiration in Total Novocaine Analgesia, Northwest Med. **30**:256 (June); 322 (July) 1931.

4. Thompson, K. W.: Spinal Anesthesia: An Experimental Study, Surg., Gynec. & Obst. **58**:852-866 (May) 1934.

of normal animals, expressed doubt whether this complication occurs in clinical spinal anesthesia. This reasoning is unsound, as is shown by the fact that I found that the minimum lethal dose of procaine hydrochloride cisternally, i. e., for the respiratory center, while relatively constant for the unanesthetized normal animal,[5] is markedly reduced by narcosis produced by large doses of morphine, moderate doses of sodium amytal,[6] dial, pentobarbital sodium and morphine and chloralose.[7] It is likewise reduced by such factors as old age, dehydration,[7] infections and low blood pressure states induced by various means.[8] This last finding is significant in view of the possibility of the spinally injected drug reaching the center after it has caused a fall in blood pressure. Of interest, too, is the work of Richet [9] on the comparative pharmacology of cocaine. He found that the sensitivity of different species of animals to cocaine increases in proportion to the increasing development of the brain.

The finding that derivatives of barbituric acid reduce the lethal dose of procaine hydrochloride is at apparent variance with the work of Hofvendahl,[10] Tatum and his co-workers,[11] LaMendola [12] and Martin.[13] These authors showed that members of the barbituric acid series are antidotes for cocaine poisoning. The discrepancy, however, is more apparent than real. In cocaine poisoning caused by systemic administration the convulsive phase is the striking feature, whereas in that caused by direct application of the drug to the nervous tissue the paralytic phase is predominant. In the former case a depressant would be indicated, and in the latter, contraindicated.

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5. CoTui, F. W.: The Intracisternal Minimum Lethal Dose of Procaine-Hydrochloride (Novocaine) in Dogs, J. Pharmacol. & Exper. Therap. **48**:223-228 (June) 1933.

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7. CoTui, F. W.: Unpublished results.

8. CoTui, F. W.: The Effect of Pathologic States on the Minimum Lethal Dose of Procaine Intracisternally, J. Pharmacol. & Exper. Therap. **50**:51-60 (Jan.) 1934.

9. Richet, C.: Les poisons convulsivants, Arch. internat. de pharmacod. **4**:293-309, 1898.

10. Hofvendahl, A.: Die Bekämpfung der Cocainvergiftung, Ztschr. f. Hals-, Nasen- u. Ohrenh. **1**:233-235, 1922.

11. Tatum, A. L.; Atkinson, A. J., and Collins, K. H.: Acute Cocaine Poisoning: Its Prophylaxis and Treatment in Laboratory Animals, J. Pharmacol. & Exper. Therap. **26**:325-335 (Dec.) 1925.

12. LaMendola, S.: Antagonismo tra sulfonale, trionale, veronale, veronale sodico, luminale sodico e cocaina, Arch. di farmacol. sper. **37**:256-268, 1924.

13. Martin, E. G.: Local Anesthetic Agents: Preventive and Emergency Treatment of Toxicity with Special Reference to Barbituric Acid Derivatives, J. A. M. A. **91**:555-557 (Aug. 25) 1928.

EFFECT OF STIMULANT ON PARALYSIS OF THE RESPIRATORY CENTER PRODUCED BY PROCAINE HYDROCHLORIDE

In view of the analeptic property of 25 per cent solution of pyridine betacarbonic acid di-ethylamide,[14] it was deemed desirable to determine its therapeutic value in animals in which the respiratory center had been paralyzed by a minimum lethal dose of procaine hydrochloride. Fifteen unanesthetized dogs were each given cisternally 1.5 mg. of procaine hydrochloride per centimeter of spinal length. This dose is a sure lethal dose.[5] It will be seen from table 1 that all the five dogs in the control group died, that two of the five in the group which were each

TABLE 1.—*Effect of a Stimulant on Unanesthetized Dogs with Paralysis of the Respiratory Center* *

Experiment No.	Weight, Kg.	Spinal Length, Cm.	Total Dose of Procaine Hydrochloride, Mg.	Dose of Stimulant Intravenously, Cc.	Result
1	14.25	74.0	111.0	0	Died
2	15.0	80.0	120.0	0	Died
3	14.5	76.0	114.0	0	Died
4	14.0	74.5	112.0	0	Died
5	18.0	81.0	121.5	0	Died
6	14.0	73.0	109.5	2	Died
7	14.0	79.0	118.5	2	Survived
8	14.5	76.0	114.0	2	Died
9	15.5	82.0	123.0	2	Died
10	16.0	76.0	114.0	2	Survived
11	15.5	82.0	123.0	5	Survived
12	16.0	86.0	129.0	5	Died
13	14.5	73.0	109.5	5	Survived
14	15.0	81.0	121.5	5	Survived
15	15.0	76.0	114.0	5	Died

* Unanesthetized dogs were given 1.5 mg. of procaine hydrochloride per centimeter of spinal length intracisternally and then a 25 per cent solution of pyridine betacarbonic acid di-ethylamide intravenously.

given 2 cc. of the pyridine betacarbonic acid de-ethylamide lived and that three of the five in the group given 5 cc. lived. Figure 1 shows the kymogram of the sixteenth animal. In this experiment the fourth ventricle was irrigated with a solution of procaine hydrochloride (1 cc. of solution to 0.8 mg. of procaine hydrochloride) until the respiration ceased. The intravenous injection of 10 cc. of the stimulant in two doses of 5 cc. each restored the respiration.

14. Faust, E. S.: On Pyridine-β-Carbonic Acid Diethylamide and Its Use as an Analeptic, Lancet **1**:1336-1339 (June 27) 1925; Ueber Pyridin-Beta-Carbonsäure-Diäthylamid (Coramin) und dessen Verwendung als Analepticum, Schweiz. med. Wchnschr. **10**:229-232 (March 6) 1924.

CHANGES IN BLOOD PRESSURE

The hypotension which accompanies spinal anesthesia has been explained in several ways. Gray and Parsons [15] attributed it to relaxation of the muscles of the abdomen and the lower limbs and to paralysis of the intercostal muscles and the consequent diminution in the pumping power of the chest. Smith and Porter [16] considered splanchnic paralysis to be the cause, as did Schilf and Ziegner.[17] Bower and his co-workers [18]

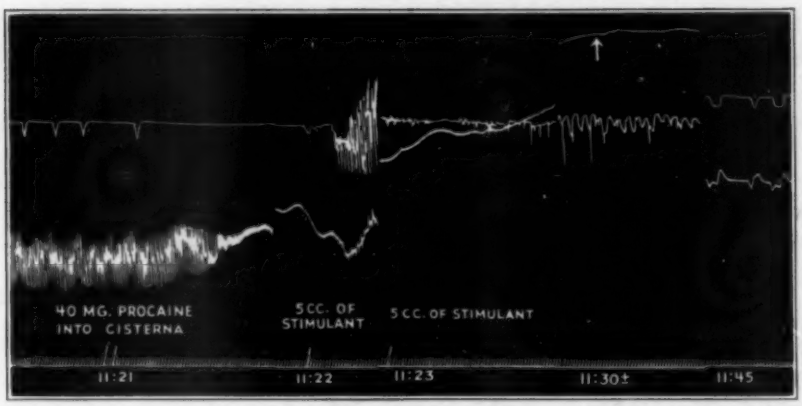

Fig. 1.—Kymogram of a dog weighing 18 Kg. and measuring 81 cm. in spinal length that was given subcutaneously 5 mg. of morphine hydrochloride per kilogram of body weight and intravenously 70 mg. of chloralose per kilogram of body weight. The upper tracing is a record of the respirations (pneumograph); the middle tracing of the blood pressure (cannula in the left femoral artery), and the lower tracing, the time in seconds. At 11:21 40 mg. of procaine hydrochloride was administered cisternally. Note the almost immediate respiratory paralysis. At 11:22 5 cc. of a 25 per cent solution of pyridine betacarbonic acid di-ethylamide in water was given intravenously. Note the respiratory movements. These are exaggerated by convulsive movements. At 11:23 a second dose of the stimulant was given. Note the rise in blood pressure and the respiratory movements at the end of the strip. In the strip made at 11:30 the arrow indicates the blood pressure (a clot formed in the cannula). Note the spontaneous respiration. At 11:45 the respirations and the blood pressure were normal.

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15. Gray, H. T., and Parsons, L. P.: Blood Pressure Variations Associated with Lumbar Puncture and the Induction of Spinal Anesthesia, Quart. J. Med. **5**:339-367 (April) 1912.

16. Smith, G. G., and Porter, W. T.: Spinal Anesthesia in the Cat, Am. J. Physiol. **38**:108-127 (July) 1915.

17. Schilf, E., and Ziegner, H.: Das Wesen der Blutdrucksenkung bei der Lumbalanesthesie, Arch. f. klin. Chir. **130**:352, 359, 1924.

18. Bower, J. O.; Clark, J. H.; Wagoner, G., and Burns, J. S.: Spinal Anesthesia, Surg., Gynec. & Obst. **54**:882-897 (June) 1932.

ascribed the fall partly to respiratory depression and partly to paralysis of the cardiac nerves. Ferguson and North [19] stated that the entire vasomotor system participates in vasodilatation and that the degree of depression of the blood pressure is in direct ratio to the number of white rami anesthetized.

My own circulatory studies are described here. Only police dogs of from 20 to 21 Kg. of body weight and of from 87 to 88 cm. in spinal length were used. These will be referred to as standard dogs. The drug was always injected into the first lumbar space in a volume of 2 cc., unless otherwise specified.

The typical blood pressure curve consists of: (1) a primary fall, (2) an intermediate rise and (3) usually a secondary fall.

These phases are shown in figure 2.

The Primary Fall.—The primary fall occurs before the injection is complete. It is accompanied by an increase in the volume of the hindleg (fig. 3) and a rise of its surface temperature, averaging 2 C. in the footpads. These changes indicate vasodilatation of the limb. This change in temperature has been shown by Morton and Scott [20] and by Gask and Ross,[21] who employed spinal anesthesia as a test of the vasomotor index of extremities with vascular disease. That the rise in surface temperature and therefore inferentially an increase in the volume of blood in the posterior extremities is effected mainly through the sympathetic nerves is evidenced by the following fact. In animals in which complete sympathectomy of one of the lower extremities has been performed, the surface temperature of that extremity is maximal after sympathectomy and does not rise further with spinal anesthesia. In the sound leg, however, the injection of the spinal anesthetic causes a prompt rise of surface temperature which soon reaches the level of that of the sympathectomized leg, as shown by figure 4.

The primary fall, then, is due to paralysis of vasomotor nerves which were reached by the original bulk of the injected fluid.

The extent of the primary fall as well as the duration is dependent more on the volume injected than on the dose of the drug. Thus, in table 2 it may be seen that 250 mg. of the drug in 2 cc. of solution produces a fall of almost the same depth and duration as 800 mg. in 2 cc.; that 250 mg. in 5 cc. produces a fall similar to 800 mg. in 5 cc.,

19. Ferguson, L. K., and North, J. P.: Observations on Experimental Spinal Anesthesia, Surg., Gynec. & Obst. **54**:621-634 (April) 1932.

20. Morton, J. J., and Scott, W. J. M.: Studies on Activity of Lumbar Sympathetic Nervous System, Ann. Surg. **92**:919-930 (Nov.) 1930.

21. Gask, G. E., and Ross, J. P.: The Surgery of the Sympathetic Nervous System, New York, William Wood & Company, 1934, p. 31.

but that the fall caused by 5 cc. of solution containing either dose is almost twice the depth and duration as with 2 cc. containing either dose. This is but to be expected since the larger the original bulk injected, the greater the number of spinal nerves paralyzed, and supra-effective concentrations cannot be more potent than already effective ones.

The Intermediate Rise.—The intermediate rise is due to vasoconstriction of the as yet unaffected part of the body in an effort to overcome the fall in blood pressure. Figure 3 shows that concomitant with the fall in blood pressure and the dilatation of the posterior extremity, there is a gradual decrease in the volume in the anterior extremity,

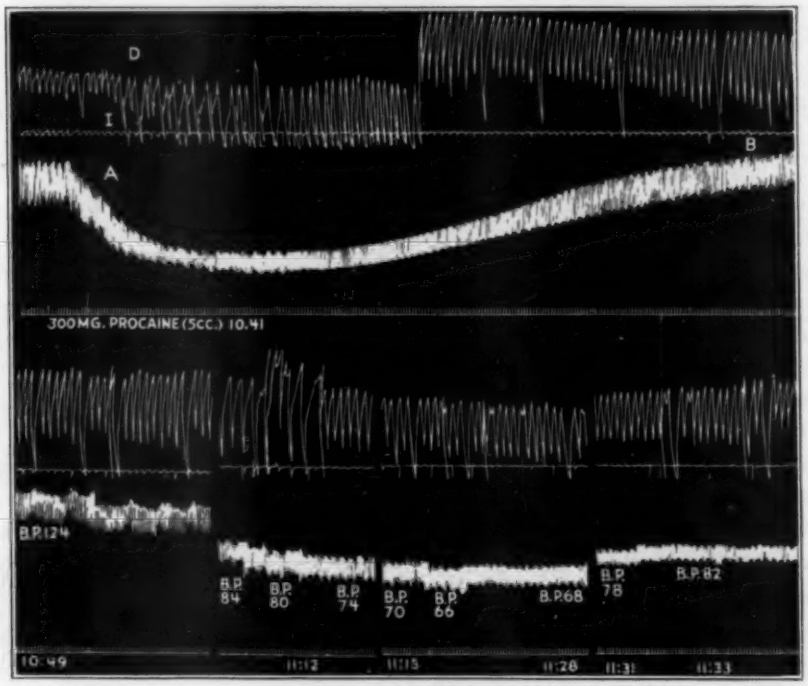

Fig. 2.—Tracing showing a typical blood pressure curve after spinal anesthesia produced by the injection of 300 mg. of procaine hydrochloride. The dog used weighed 19 Kg. and measured 87 cm. in spinal length. At 9:45 5 mg. of morphine hydrochloride per kilogram of body weight was given subcutaneously. Diaphragmatic breathing was recorded by a lever attached to the abdominal wall and is shown in tracing *D*. I is the intercostal tracing made with a thoracic pneumograph. The blood pressure was registered from the left femoral artery. In the strip made at 10:41 note the primary fall at *A* and the intermediate rise at *B*. At 10:49 the secondary fall is beginning. At 10:49, 11:12 and 11:15 the secondary fall is recorded. Note the trough of the fall to 68 mm. at 11:28. The strip made at 11:31 and 11:33 shows recovery of the blood pressure.

which reaches its maximum with the peak of the intermediate rise. The injection of a larger volume of the drug apparently reached a sufficiently high level to paralyze the vasoconstrictors of the anterior extremity, shown in figure 3, made at 3:50 and later. No compensatory rise was evident. Also, flooding the nerves along the entire length of the spinal canal with the anesthetic solution abolishes the compensatory rise, as is shown in figure 5. This compensatory effort is probably brought about by the carotid sinus and aortic nerve mechanism. The completeness of the compensation depends on the extent and the efficiency of the as yet unaffected vasomotor nerves, since the peak of the intermediate rise is lower with larger than with smaller injected volumes.

The injected volume remaining equal, the kind of premedication determines the rapidity of the intermediate rise. Thus, it is slowest with morphine and ether, next with sodium amytal, pentobarbital sodium

TABLE 2.—*Comparative Effect of Dose and Volume of Drug Injected on the Blood Pressure*

Experiment No.	Dose of Procaine Hydrochloride, Mg.	Volume Injected, Cc.	Initial Blood Pressure Mm. of Hg	Lowest Blood Pressure (Primary Fall), Mm. of Hg	Time from Injection to Crest of Intermediate Rise, Sec.
1	800	2	125	90	100
2	250	2	115	86	80
3	800	5	120	50	210
4	250	5	110	54	180

and morphine and chloralose and most rapid with dial and ethyl carbamate. This probably means that the reactiveness of the sympathetic system to a fall in blood pressure is modified by the preliminary administration of the narcotic. Stated in other words, the efficiency of the compensatory mechanism is impaired in different degrees by different narcotics.

The Secondary Fall.—With smaller doses of the drug the secondary fall may be absent. It begins from five to twenty-five minutes after the injection and lasts for a more prolonged period than the two previous phases. It is ascribed to the gradual spread of the drug upward, paralyzing the vasomotor nerves one by one so that not enough of the body is left unparalyzed to maintain a normal blood pressure. The relation of the dose to the extent of the fall and the duration of the period before the blood pressure is restored to the 100 mm. level is shown by table 3. The extent of the secondary fall is also related to the position of the animal. The dose and volume remaining the same, the secondary fall is deepened and prolonged by the Trendelenburg position, as may be

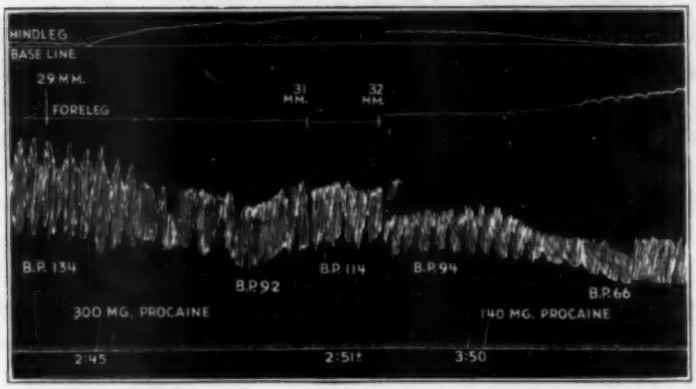

Fig. 3.—Kymogram of a dog weighing 21 Kg. and measuring 89 cm. in spinal length. At 2:45 when the initial blood pressure was 134, 300 mg. of procaine hydrochloride in 2 cc. of water was injected into the spinal canal at the twelfth thoracic space. Note that concomitant with the primary fall there is an increase in the volume of blood in the hindleg and a decrease in that of the foreleg. The decrease in the volume of blood of the foreleg is maximal at 2:51, the peak of the intermediate rise. At 3:50 140 mg. of procaine hydrochloride in 5 cc. of water was injected into the same space. Note the further fall in the blood pressure, an increase in the volume of blood in the foreleg and a decrease of that in the hindleg parallel with the blood pressure.

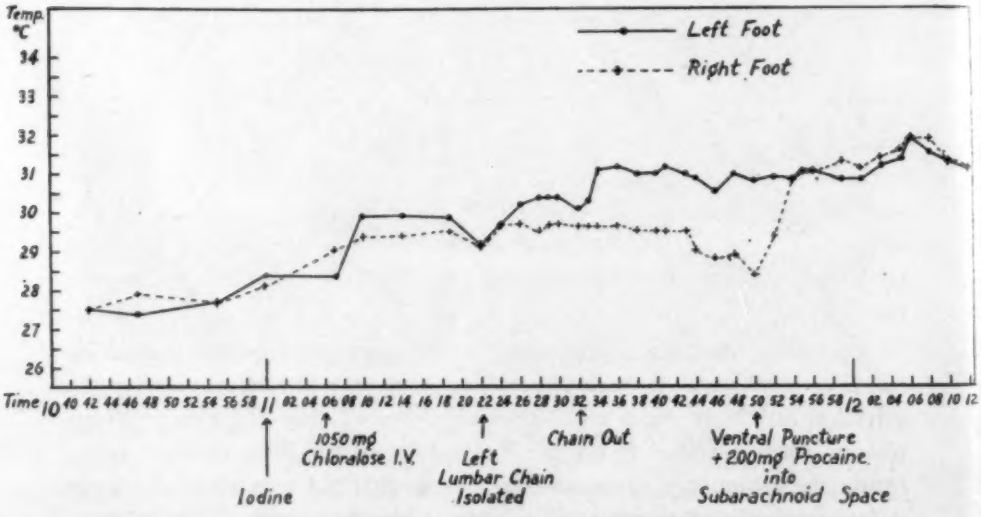

Fig. 4.—Curves showing temperature response caused by sympathectomy in dog 22, a female, weighing 15 Kg. Morphine hydrochloride, 5 mg. per kilogram of body weight, was administered subcutaneously and chloralose, 70 mg. per kilogram of body weight, intravenously. Note (1) the rise in surface temperature of both extremities after the administration of chloralose intravenously, (2) the rise in the surface temperature of the left footpad on isolation of the left lumbar chain and the further rise when the chain was removed, (3) and the rise in surface temperature of the right footpad after spinal anesthesia.

seen in table 4. This result is to be expected, since the Trendelenburg position allows a more cephalad spread of a hyperbaric solution.

Comment.—This typical curve is modified by the occurrence of respiratory paralysis. The blood pressure in this case describes a fairly swift arc to zero (fig. 6). This paralysis may occur in any of the three phases. Artificial respiration restores it to its level previous to the occurrence of this complication (fig. 6). This swift fall of blood

TABLE 3.—*Relation of the Dose of the Drug to the Fall in Blood Pressure and Length of Period Before Recovery*

Experiment No.	Total Dose of Procaine Hydrochloride, Mg.	Lowest Blood Pressure, Mm. Hg	Time of Recovery to 100 Mm. Hg, Min.
1	250	96	52
2	300	68	74
3	600	52	106
4	700	36	134
5	800	22	192

* Morphine sulfate (2 mg. per kilogram of body weight subcutaneously) and ether were given preliminary to the administration of the spinal anesthetic.

TABLE 4.—*Relation of Position to Secondary Fall in Blood Pressure*

Head Down		Horizontal	
Initial Blood Pressure, Mm. of Hg	Minimum Blood Pressure, Mm. of Hg	Initial Blood Pressure, Mm. of Hg	Minimum Blood Pressure, Mm. of Hg
120	80	118	96
100	76	102	86
116	72	114	78
125	86	125	92
102	72	102	82
108	76	108	84
112	78	110	78
112	76	112	84

* Dogs weighing 20 Kg. and measuring 88 cm. in spinal length were each given 400 mg. of procaine hydrochloride in 3 cc. of water intraspinally.

pressure will be explained in the section on the administration of carbon dioxide.

That this pattern of blood pressure curve is not identical with that obtained on human beings during spinal anesthesia may be seen by comparing it with figure 7. Whether the transience of the primary fall is missed in the intermittent method of sphygmomanometry or whether the difference in the curvatures of the human and canine spines accounts for the divergence has not as yet been ascertained but is being investigated.

As evidence of splanchnic dilatation, changes in intestinal volume are not reliable. For while the vessels themselves may undergo dilatation, the intestinal muscle undergoes contraction in response to the release of sympathetic inhibition, thus bringing two opposing factors into play. A better index of splanchnic dilatation is given by changes in the size of the spleen. This organ was shown by Barcroft [22] to be one of the principal visceral organs for circulatory homeostasis. It dilates in time of rest to accommodate excess blood and contracts in time of emergency to expel blood into the circulation. According to Buljak [23] and Schafer

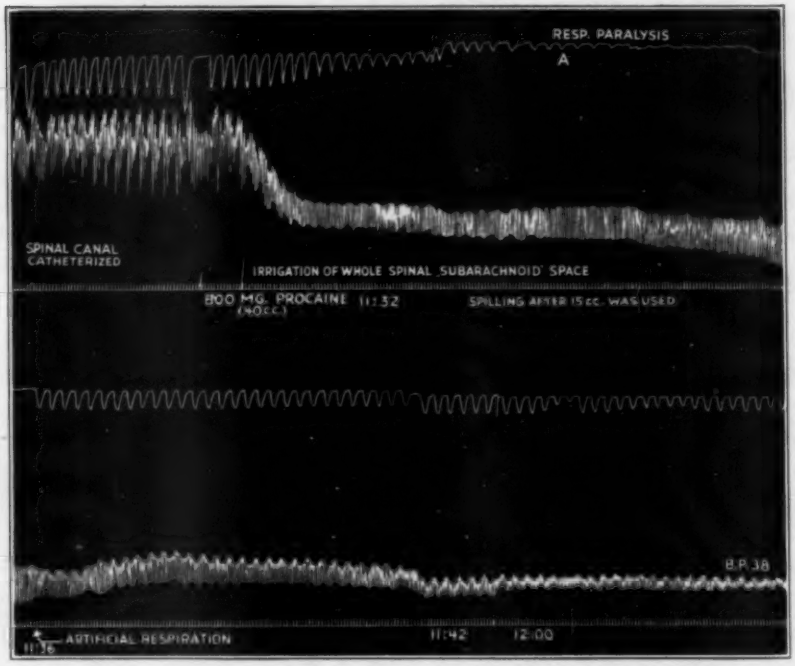

Fig. 5.—Tracing showing the absence of an intermediate rise by irrigation of the entire spinal subarachnoid space with procaine hydrochloride. The dog used weighed 18 Kg. and measured 86 cm. in spinal length. At 10:45 5 mg of morphine sulfate per kilogram of body weight was administered subcutaneously. At 11:00 ether was started. At from 11:08 to 11:28 the cisterna magna was opened and the spinal subarachnoid space was catheterized with a ureteral catheter. Respiratory paralysis supervened at *A* and modified the curve somewhat. At 11:36 there was a slight rise after artificial respiration and at 11:42, the usual secondary fall.

22. Barcroft, J.: Recent Knowledge of the Spleen, Lancet **1**:319-322 (Feb. 11) 1925.

23. Buljak, J.: Ueber die Contractionen und die Innervation der Milz. Virchows Arch. f. path. Anat. **69**:181-213, 1877.

and Moore [24] it is supplied by vasoconstrictors from the third thoracic to the first lumbar segment, chiefly from the fifth to the tenth thoracic segment.

Normally, as may be seen from table 5, the mean ratio of splenic weight to body weight is 1.3 to 2.7 $\times$ 10^{-3}. In spinal anesthesia, the spleen becomes from four to five times its normal size. Figure 8 shows a section of the spleen before spinal anesthesia, and figure 9, one after spinal anesthesia. Note that the latter is packed with red blood cells. Figure 10 shows three views of the same spleen under the following

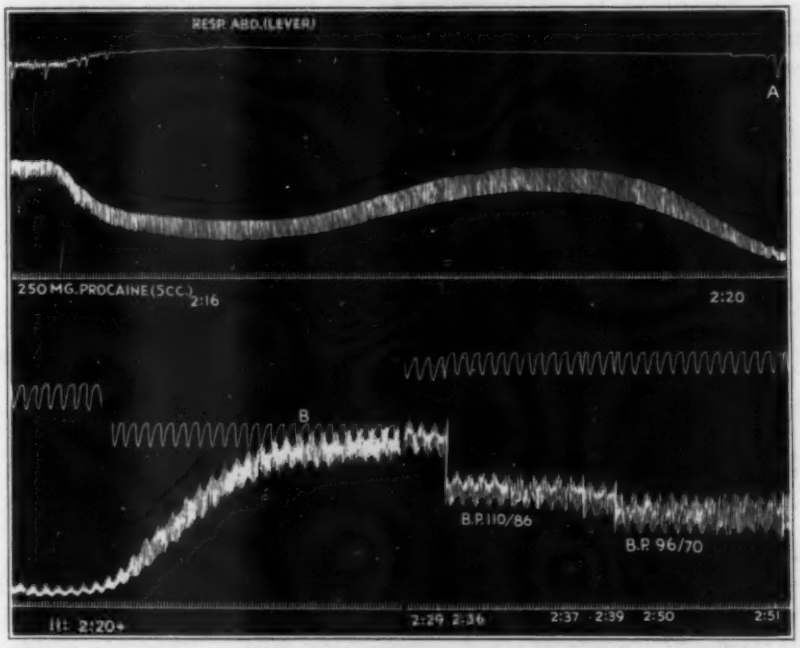

Fig. 6.—Tracing showing the modification of the typical blood pressure curve by respiratory paralysis. The dog used weighed 16 Kg. and measured 84 cm. in spinal length. At 1:50 5 mg. of morphine per kilogram of body weight was administered subcutaneously. At 2:08 ether was started. In the strip made at 2:16 note the primary fall and intermediate rise. Note the gradual fall after complete respiratory paralysis. Artificial respiration was started at *A*. In the strip made at 2:20 note the rise in blood pressure at *B* to above normal. The abdominal lever was readjusted here and in the next tracing. At 2:29 there was a secondary fall.

conditions: (*a*) after medication with morphine and chloralose, (*b*) after spinal anesthesia and (*c*) after the intravenous injection of 1 mg.

24. Schafer, E. S., and Moore, B.: On the Contractivity and Innervation of the Spleen, J. Physiol. **20**:1-50 (June) 1896.

of ephedrine hydrochloride per kilogram of body weight. It is thus shown that the splanchnic vessels also undergo vasodilatation.

As to whether the abolition of the respiratory excursions of the thorax as a result of intercostal paralysis is responsible for the fall in blood pressure, the following experiment devised for another purpose by Dr. E. A. Rovenstine is interesting. The lungs of a dog under morphine and chloralose anesthesia were irrigated through a tracheal tube with pure oxygen until complete apnea was produced. It is seen (fig. 11) that there is no fall in blood pressure with the cessation of respiratory movements. The component which the thoracic excursions contribute to the homeostasis of blood pressure is at best a minor one, and with a normally functioning vasomotor mechanism the effect of its absence is negligible.

The question of the cause of the fall in blood pressure may now be answered. It is due to the paralysis of the vasomotor nerves of

TABLE 5.—*Effect of Spinal Anesthesia on the Spleen*

Weight of Spleen*	
Normal	Under Spinal Anesthesia
2.69	10.67
2.36	7.3
2.2	14.6
2.3	8.5
1.3	14.8
2.8	
1.8	Average 11.17
2.2	
Average 2.27	

* To obtain body weight ratio multiply the ratio by 10^{-3}.

the segments anesthetized, with the consequent dilatation of the vessels, somatic as well as visceral. The resulting increase of the vascular tree makes the existing blood volume inadequate. Thoracic paralysis may contribute its share in the latter part of the anesthesia, either through abolition of the suction effect of the chest or through an accumulation of carbon dioxide. But this is not primary and may at best be only a contributory factor. Neither can the paralysis of the cardiac nerves be considered primary or immediate, as hypothecated by Bower and his co-workers.[18] The fact that only in those of their cases in which the level of anesthesia has reached the level of the cardiac nerves is there a marked fall in pressure is inconclusive evidence that it is primarily the paralysis of the cardiac nerves which causes the low blood pressure. It only means that more vasomotor nerves are paralyzed and the less unaffected nerves are left to compensate for the fall.

EFFECTS OF THE LOW BLOOD PRESSURE

In this set of experiments, standard animals were given 5 mg. of morphine hydrochloride per kilogram of body weight subcutaneously fifteen minutes before they were put on the experimental table. There they were anesthetized lightly with ether while the femoral artery was being cannulated for measurement of the blood pressure and lumbar puncture performed, both procedures together taking less than fifteen minutes. The administration of ether was discontinued, and the animal was allowed to lie quietly for ten minutes. A control set of blood samples was then taken. The spinal anesthetic was injected, and the blood pressure was allowed to fall gradually to below 80 mm. Artificial respiration was started so as to avoid any asphyxia. After the blood pressure had been under 80 mm. for an hour, the second set of blood samples was taken. Arterial oxygen and venous oxygen and lactic acid were determined from the blood samples.

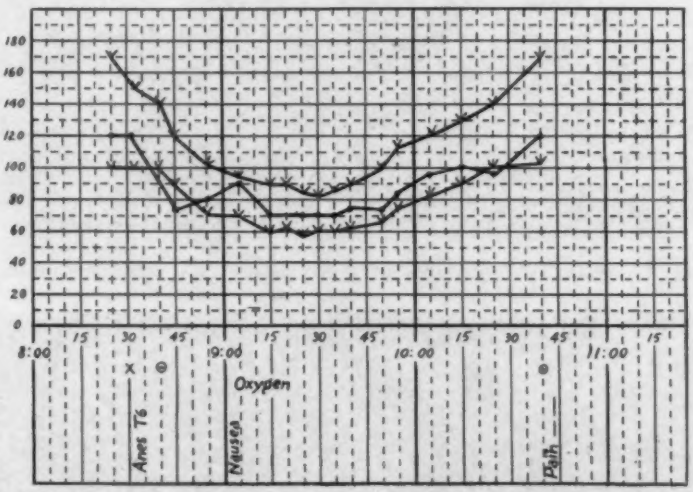

Fig. 7.—The blood pressure curve during spinal anesthesia in a clinical case, in which amputation of the cervix, repair of a cystocele and perineorrhaphy were performed (adapted from Waters and Rovenstine). The following code is used: the solid dot, the pulse rate; the circle, the respiratory rate; *V*, the blood pressure; the circle and dot, operation; and *X*, anesthesia.

Table 6 shows that in the hypotension of spinal anesthesia, even though the oxygen content of the arterial blood may be slightly raised by artificial respiration, there is a lowered oxygen content of the venous blood. This finding corresponds with that of Aub and Cunningham [25] in experimental traumatic shock. On account of the sluggish circulation due to the low blood pressure, oxygen is not delivered in sufficient

25. Aub, J. C., and Cunningham, T. D.: Studies in Experimental Traumatic Shock: II. The Oxygen Content of the Blood, Am. J. Physiol. **54**:408-415 (Dec.) 1920.

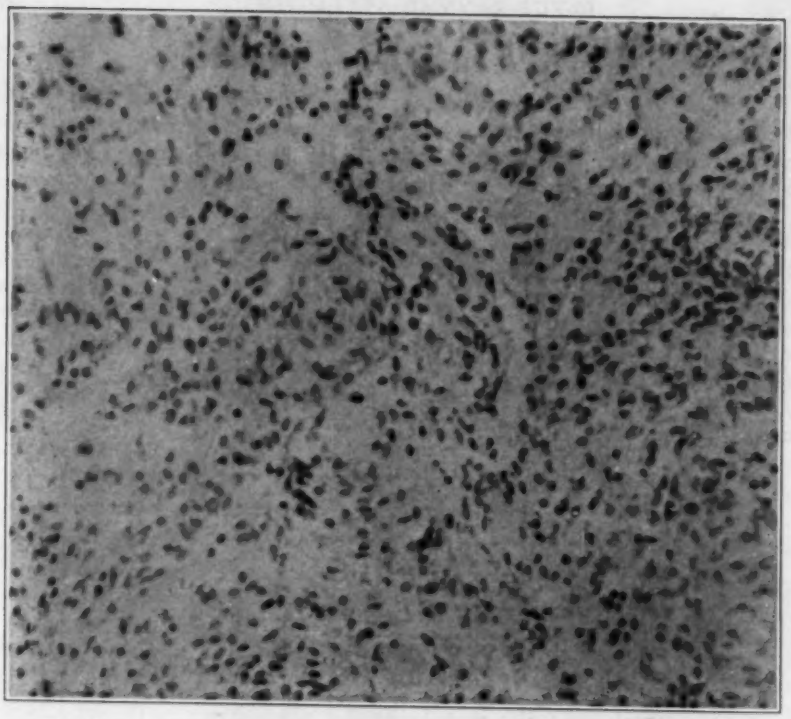

Fig. 8.—Section of the spleen of a dog before light ether anesthesia.

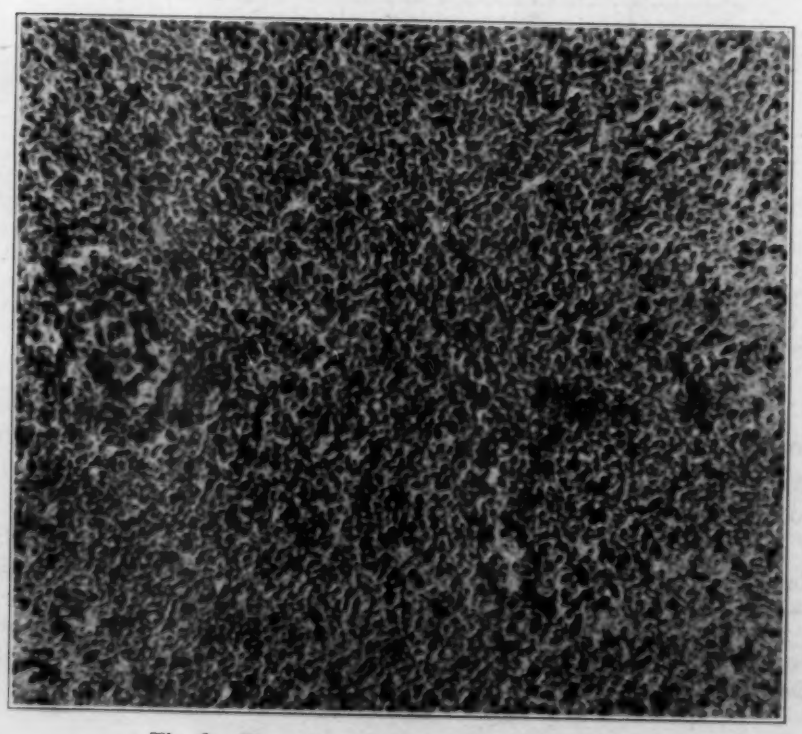

Fig. 9.—The same spleen after spinal anesthesia.

amount to the tissues; that is, there is tissue asphyxia. The venous blood, having come into oxygen equilibrium with the tissues, reflects this anoxia. The anoxia is also reflected in the tissue metabolism. Normally, glycogen is broken down into lactic acid, which is partly reconverted into glycogen and partly oxidized into carbon dioxide and water, both processes necessitating oxygen. Anoxia leads to an accumulation of lactic acid in the blood. As will be seen from the table, the low blood pressure is accompanied by such an increase in blood lactic acid. This result explains the finding of Saklad [26] of decreased carbon dioxide-combining power of the blood during spinal anesthesia.

In three control animals which were given morphine and ether in a similar way and 800 cc. of a 1 per cent solution of procaine hydro-

TABLE 6.—*Effect of the Hypotension of Spinal Anesthesia on the Arterial Oxygen Content*

Experiment No.	Time	Blood Pressure, Mg. of Hg	Arterial Oxygen, Volumes %	Venous Oxygen, Volumes %	Lactic Acid, Mg. per 100 Cc.
1	10:15	120	22.9	19.7	
	11:40	50 1 hr.	23.9	6.5	
	12:55	Above 80 1 hr.	....	15.8	
2	9:52	118	22.8	13.0	
	11:12	65 1 hr.	22.1	10.1	
3	9:55	115	15.8	12.5	
	10:03	Artificial respiration started			
	10:11	118	23.0	12.7	
	11:57	50 1 hr.	19.0	5.8	
4	10:01	108	21.0	16.8	35.0
	11:36	60 45 min.	22.0	7.4	45.0
5	10:16	128	21.8	20.0	28.5
	11:58	60 70 min.	21.7	10.9	45.0
	2:00	Above 80 105 min.	21.7	14.7	29.0
6	11:06	115	20.9	17.7	34.0
	1:55	40 1 hr.	19.6	9.5	84.0

chloride subcutaneously, there was a slight rise in the lactic acid content due to the light ether narcosis. This rise was fairly constant throughout and did not increase after the subcutaneous injection of procaine hydrochloride.

The reduction of cardiac output in spinal anesthesia found by Burch and Harrison,[27] the diminished ability to endure hemorrhage found by Burch, Harrison and Blalock [28] and the presence of stagnant anoxia found in this work are parts of the picture of what has been called

26. Saklad, M.: Studies in Spinal Anesthesia, Am. J. Surg. **11**:452-460 (March) 1931.

27. Burch, J., and Harrison, T. R.: The Effect of the Administration of Fluid on the Fall in Blood Pressure Caused by Spinal Anesthesia, Arch. Surg. **22**:1045-1046 (June) 1931.

28. Burch, J.; Harrison, T. R., and Blalock, A.: A Comparison of the Effects of Hemorrhage Under Ether Anesthesia and Under Spinal Anesthesia, Arch. Surg. **21**:693-697 (Oct.) 1930.

neurogenic shock. Labat [29] and Koster and Kasman [2] have taught that even if the blood pressure falls to such a low point as not to be measurable, the fall is harmless. Their basis for this belief is that in a large number of cases in which spinal anesthesia was used they have not had

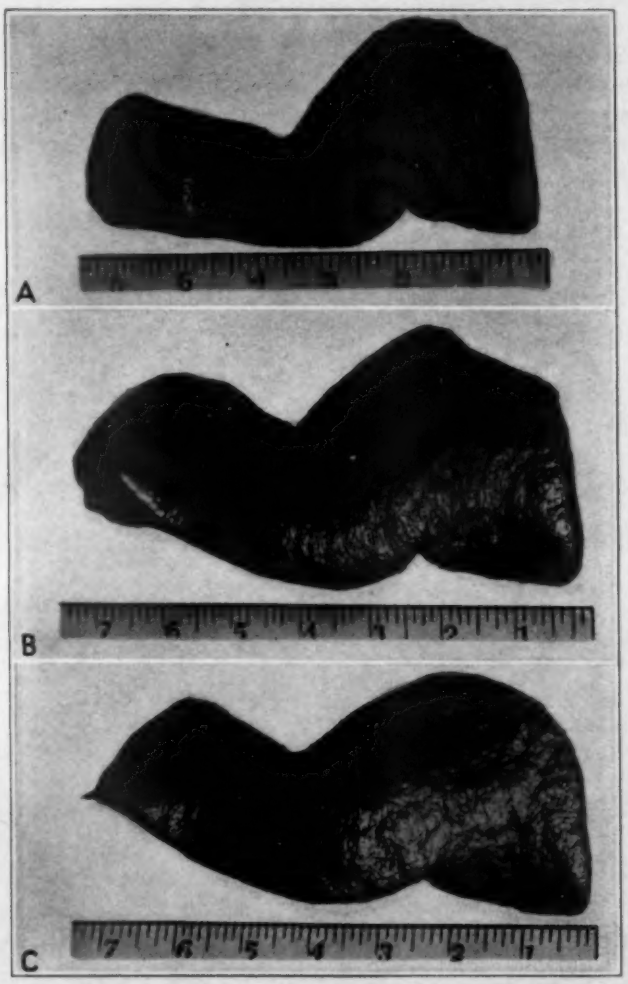

Fig. 10.—Three views of the spleen shown in figures 8 and 9. The dog was given premedication with morphine and chloralose. Procaine hydrochloride, 300 mg. in 3 cc. of water, was injected into the first lumbar space. In *A* there is some degree of splenic dilatation with the premedication; in *B* there is marked dilatation after spinal anesthesia, and in *C*, marked contraction of the spleen after the administration of ephedrine. In *B* note the marked curling at the upper margin and also the widening and thickening.

29. Labat, G.: Regional Anesthesia, Philadelphia, W. B. Saunders Company, 1924, p. 459.

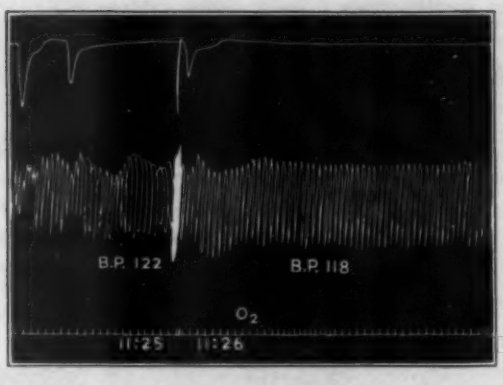

Fig. 11.—Tracing made on a dog weighing 12 Kg. that was given 5 mg. of morphine hydrochloride per kilogram of body weight subcutaneously, 70 mg. of chloralose per kilogram of body weight intravenously and tracheal irrigation of pure oxygen. Note the apnea and maintenance of the blood pressure.

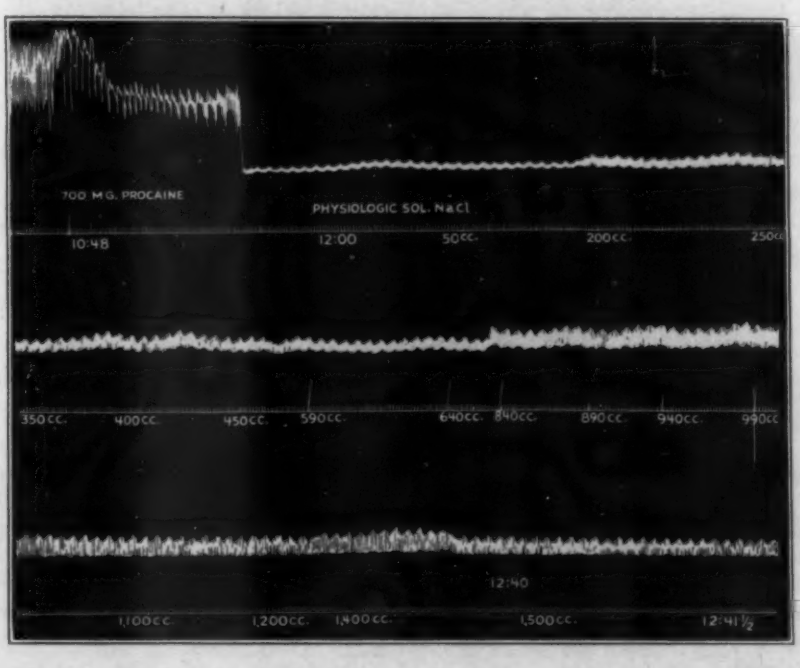

Fig. 12.—Tracing showing the effect of infusion of physiologic solution of sodium chloride in shock due to spinal anesthesia. The dog used weighed 19 Kg. and measured 87 cm. in spinal length. Dial and ethyl carbamate were used for narcosis. Note that infusion of even 1,500 cc. did not raise the level of the blood pressure.

a fatality. But death cannot be a valid criterion of whether or not harm is done, for the margin of safety in the animal organism is so wide that a great deal of injury can occur without producing death.

TREATMENT OF THE SHOCK DUE TO SPINAL ANESTHESIA

An effort was made to determine experimentally the comparative efficacy of the usual measures for combating shock due to spinal anesthesia, namely, the intravenous injection of saline solution, the transfusion of blood, the injection of ephedrine and the Trendelenburg position.

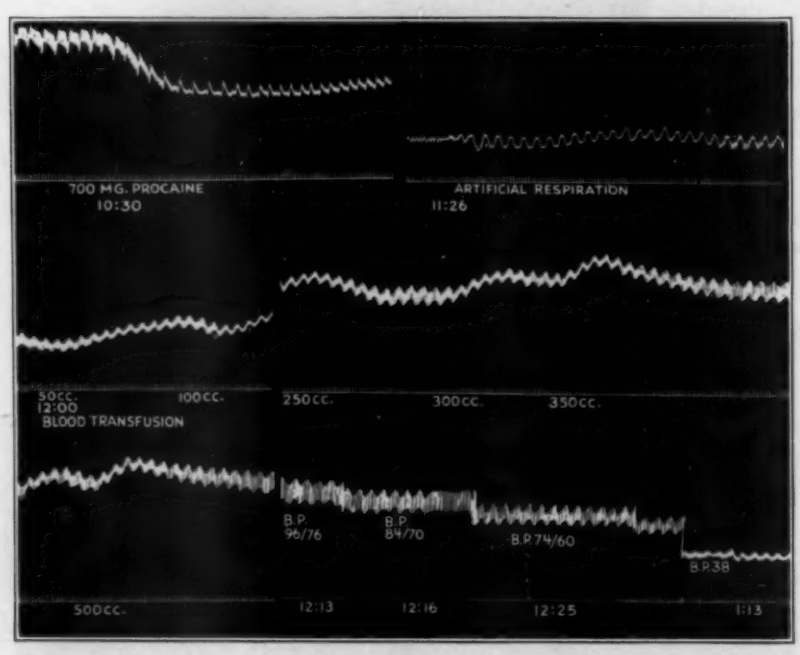

Fig. 13.—Tracing showing the effect of blood transfusion on an animal in shock due to spinal anesthesia. The dog used weighed 19 Kg. and measured 87 cm. in spinal length. At 10:05 5 mg. of morphine per Kg. of body weight was administered subcutaneously. At 10:20 ether was given and was discontinued at 10:27. In the strip made at 11:26 note that artificial respiration did not improve the blood pressure. In the strip made from 12:00 to 12:15 note that 500 cc. of blood, while raising the pressure during the injection, did not keep it from falling back to below shock level after the transfusion was discontinued.

In the experiment depicted in figure 12 physiologic solution of sodium chloride was injected into an animal in shock due to spinal anesthesia in quantities as large as the calculated total blood volume of the animal. This caused a transient rise in blood pressure, lasting as long as the infusion was continued, but soon

falling again to its previous level. In figure 13 it is shown that while blood transfusion causes a somewhat higher and longer rise, it is also inadequate.

The effect of ephedrine in this form of shock was studied in three sets of experiments. In a set of nine control experiments with spinal anesthesia it was found that in standard dogs from 700 to 800 mg. of procaine hydrochloride injected spinally caused a secondary fall so prolonged and profound that it required two hours or more after the blood pressure fell below 80 mm. to recover to 100 mm. It was also found in a series of six normal dogs used for timing the effect of ephedrine that a dose of 2 mg. of ephedrine hydrochloride per kilogram of body weight caused a rise lasting from forty-five minutes to one hour.

In the interval between the forty-five minutes to one hour and the two hours necessary for the recovery of blood pressure, there is over an hour in which to determine whether ephedrine actually improves the circulation or whether, like the infusion of physiologic solution of sodium chloride and of blood, it leaves the circulation without any material improvement after its effect is over.

In eight standard animals it was found that the intravenous injection of this dose of ephedrine hydrochloride within the first five to ten minutes after the blood pressure reached shock level caused the blood pressure to maintain its level of over 100 mm. from one and one-half to two hours after the injection of ephedrine, that is, until recovery. The tracings in figure 14 are representative for this experiment.

The reason for these results is obvious. The state of shock produced by spinal anesthesia is due primarily to the loss of nervous regulation of the peripheral circulation. To correct this by increasing the amount of fluid meets with two difficulties—the increase in the exudation of fluids into the tissue spaces and the great increase in the volume of the vascular bed. Ephedrine, however, because of its sympathetico-mimetic action, is a substitute for the lost nervous regulation and is therefore more effective. As may be seen from the spleen shown in figure 10 *C*, in which ephedrine produced contraction, and from figure 15, which shows a contraction of the posterior extremity in spinal anesthesia in response to ephedrine, this drug acts on organs affected by spinal anesthesia. This is to be expected as ephedrine, like epinephrine, acts on the so-called myoneural junctions of the sympathetic nerves distal to the point of the effect of spinal anesthesia.

Figure 16 shows the kymogram of a dog in shock due to spinal anesthesia. Fifteen minutes after the development of the shock, the dog was placed in the Trendelenburg position. The lowering of the head caused a rise of some 20 mm. of blood pressure lasting for less than a minute and falling again to the previous level. This is to be anticipated, as the raising of the distal part of the body drives the blood accumulating in the distal veins toward the heart, thereby increasing its output for the moment. But there is no lasting improvement in the circulation. The head-down position in other forms of shock is useful because this transient improvement causes an improvement in the

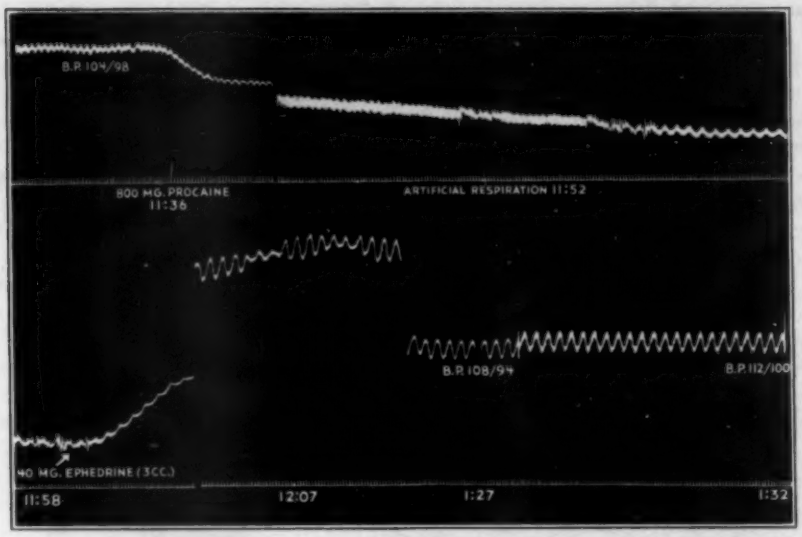

Fig. 14.—Tracing showing the efficacy of ephedrine if given early during shock due to spinal anesthesia. The dog used weighed 20 Kg. and measured 88 cm. in spinal length. At 11:02 5 mg. of morphine per kilogram of body weight was administered subcutaneously. At 11:25 ether was started and was discontinued at 11:32. At 11:58 2 mg. of ephedrine per kilogram of body weight was administered intravenously. At 12:07 the blood pressure was almost 200 mm. From 1:27 to 1:32 the blood pressure stayed over 100 mm., even after the effect of the ephedrine.

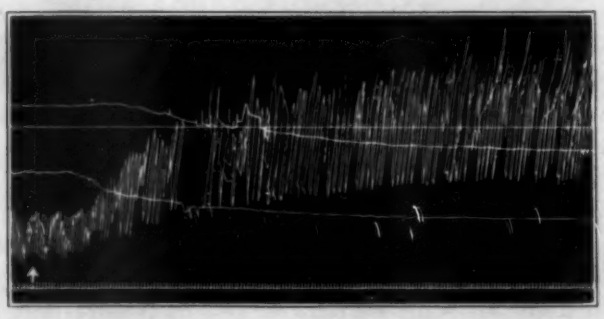

Fig. 15.—Same experiment as that shown in figure 3. The upper tracing shows the volume of blood in the hindlimb; the next tracing, the base line; the third tracing, the volume of blood in the foreleg, and the fourth, the blood pressure curve. The bottom tracing shows the time in seconds. At the time marked by the arrow, 1 mg. of ephedrine hydrochloride was injected intravenously. Note the decrease in the volume of both limbs and the rise in blood pressure.

medullary centers, which is reflected in an increased tone of the circulation, which, in turn, improves the centers further, thus breaking the vicious circle. But in order that this improvement may occur, the nerve pathway to the circulatory system, namely, the vasomotor nerves, must be intact. In spinal anesthesia these nerves are paralyzed, and the measure is therefore futile.

The danger of the Trendelenburg position when hyperbaric solutions are used is seen in the following three sets of experiments recorded in table 7.

The animals were all matched as to weight and spinal length. The drug was dissolved and made up to 3 cc. in distilled water and then injected into the first

TABLE 7.—*Effect of Trendelenburg Position*

Position	Weight, Kg.	Spinal Length, Cm.	Total Dose of Procaine Hydrochloride, Mg.	Specific Gravity of Solution at Room Temperature	Result
Horizontal	21	88	700	1.032	Survived
	20	88	700	.....	Survived
	19	88	700	.....	Survived
	19	87	800	1.039	Survived
	19	87	800	.....	Survived
	20	88	900	.....	Died in 26 min.
	21	88	900	.....	Died in 30 min.
	19	87	850	.....	Died in 35 min.
Head down 17°	19	87	600	1.029	Died in 17 min.
	20	87	500	1.026	Died in 15 min.
	20	88	400	1.018	Died in 16 min.
	21	88	400	.....	Died in 18 min.
	19	88	400	.....	Died in 20 min.
	19	88	350	1.016	Survived
	20	88	350	.....	Survived
	19	87	300	.....	Survived
Head up 17°	20	88	900	.....	Survived
	20	88	1,000	1.052	Survived
	20	88	1,000	.....	Survived
	20	88	900	.....	Survived
	21	88	900	.....	Died in 55 min.
	20	88	1,000	.....	Died in 50 min.
	21	89	1,000	.....	Died in 45 min.

lumbar interspace in from nine to ten seconds. In the first series the animals were kept in the horizontal position; in the second, they were in the head-down position at an angle of 17 degrees, and in the third, they were in the head-up position at the same angle. Each animal was anesthetized with 50 mg. of pentobarbital per kilogram of body weight intravenously, preliminary to the spinal injection.

The table shows that with the animal in the horizontal position it takes over 850 mg. of procaine hydrochloride to cause death in the animals by respiratory paralysis in an average time of thirty minutes. With the animal in the head-up position, from 900 to 1,000 mg. causes death in an average time of fifty minutes. When the head-down position was used, however, only 400 mg. was necessary to cause death in an average time of seventeen minutes. A recent paper by Grodinsky

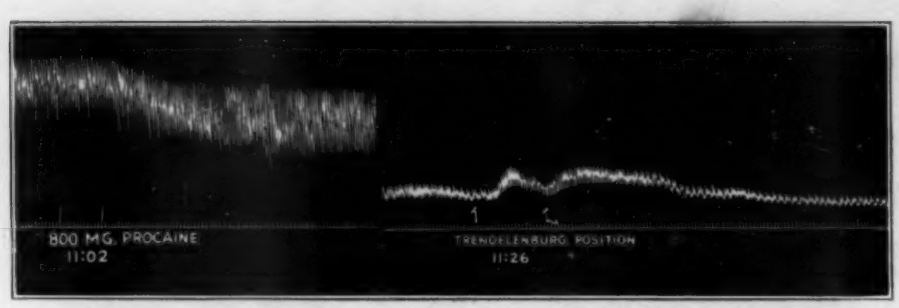

Fig. 16.—Tracing showing the effect of the Trendelenburg position on an animal in shock due to spinal anesthesia. The dog used weighed 20 Kg. and measured 88 cm. in spinal length. At 10:50 dial and ethyl carbamate were given intraperitoneally (50 mg. per kilogram of body weight). In the strip made at 11:02 note the slight primary fall. At 11:26 the Trendelenburg position was assumed in two stages (corresponding to the time marked by the two arrows). Note the slight rise and the gradual fall to a previous level or even lower.

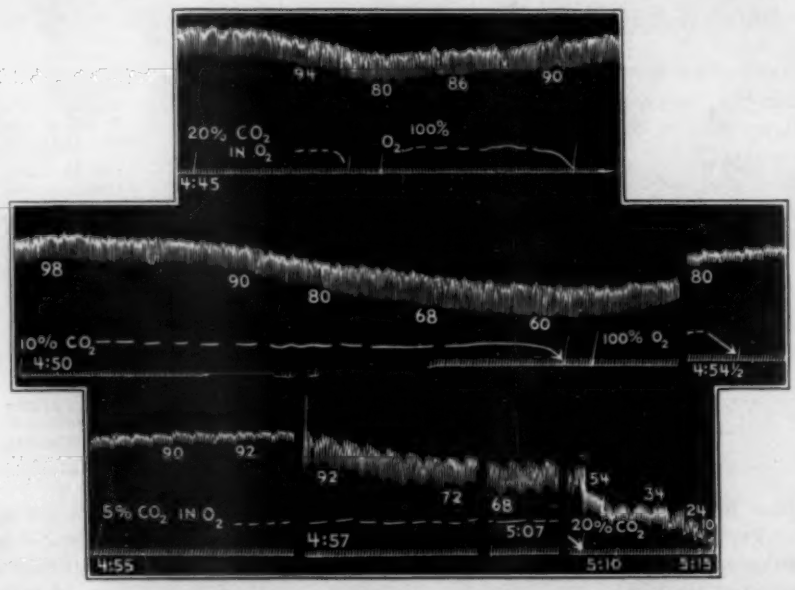

Fig. 17.—Tracings showing the effect of different concentrations of carbon dioxide and oxygen on the blood pressure. The dog used weighed 18 Kg. Morphine hydrochloride, 5 mg. per kilogram of body weight was administered subcutaneously and chloralose, 70 mg. per kilogram of body weight, intravenously. At 4:30 300 mg. of procaine hydrochloride was given intraspinally. At 4:45 20 per cent of carbon dioxide in oxygen was given. Note the prompt fall of blood pressure and the rise again on inhalation of oxygen. At 4:50 10 per cent of carbon dioxide in oxygen was given. Note the longer latent period before the fall in blood pressure. At 4:54½ there is a gradual rise with 100 per cent oxygen. At 4:55 5 per cent of carbon dioxide in oxygen was administered. Note the still longer latent period. At 5:10 the animal was killed with 20 per cent carbon dioxide.

and Baker [30] showing that the head-down position of the cadaver caused a more cephalad spread of dyes injected into the spinal subarachnoid space lends support to this result. In all the dogs dying from respiratory paralysis, procaine hydrochloride was demonstrated qualitatively in the cisternal fluid after death. A study reported elsewhere [31] of the phenomenon of the gravitation current when a fluid of greater is injected into one of lesser density and the system placed on an incline will aid in explaining why a larger lethal dose is required in the horizontal than in the head-down position. For, whereas a rapid flow to the medulla assures the arrival of the drug there in a relatively high concentration, a slow spread by molecular diffusion allows absorption, dilution, fixation and probably destruction.

THE USE OF CARBON DIOXIDE

Carbon dioxide has been misused as a respiratory or circulatory stimulant in spinal anesthesia. Heymans and his co-workers [32] have shown that it is contraindicated as it lowers the blood pressure further by its action on the peripheral vessels. CoTui, Rovenstine and McCloskey [33] have confirmed this and extended the study. Figure 17 shows the kymogram of a dog in spinal anesthesia under different concentrations of carbon dioxide and oxygen. The explanation of this seeming paradox is simple. When the sympathetic system is intact, the administration of carbon dioxide causes a centrally mediated general vasoconstriction, which raises the blood pressure. But when these nerves are paralyzed, the peripheral action predominates, causing vasodilatation and therefore a further lowering of blood pressure.

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30. Grodinsky, M., and Baker, C. P.: Spinal Anesthesia: A Clinical and Experimental Study, Surg., Gynec. & Obst. **57**:187-205 (Aug.) 1933.

31. CoTui, F. W.: Further Studies in Subarachnoid Anesthesia, Anesth. & Analg. **13**:143-151 (July-Aug.); 183-192 (Sept.-Oct.) 1934.

32. Heymans, C.; Bouckaert, J. J., and Bert, P.: Mécanisme du collapsus circulatoire: Influences des traumatismes et de la rachianesthésie sur les réflexes circulatoires sino-carotidiens, Compt. rend. Soc. de biol. **112**: 714-716 (Feb. 24) 1933.

33. CoTui, Rovenstine and McCloskey: Unpublished results.

CONGENITAL ABNORMAL ARTERIOVENOUS ANASTOMOSES OF THE EXTREMITIES

WITH SPECIAL REFERENCE TO DIAGNOSIS BY ARTERIOGRAPHY AND BY THE OXYGEN SATURATION TEST

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AND
WILLIAM M. McCORD, PH.D.
NEW ORLEANS

Arteriovenous fistula was first mentioned in the literature in 1757, when William Hunter [1] described the clinical features of the condition and the disturbed vascular physiology associated with it. In 1762 he reported the two cases, in both of which the condition was discovered by chance during phlebotomy, on which his description was based. A few years later Delacombe confirmed his observations at autopsy, and since that time a voluminous literature has grown up about the subject, most of which, however, concerns the traumatic or acquired variety.

The congenital variety has always been regarded as decidedly infrequent. Of four hundred and forty-seven cases reports of which were collected by Callander [2] in 1920 at the instigation of Halsted, only three fell into this category, and as late as 1930 Lewis [3] was able to find in the literature reports of only twenty-four cases, to which he added six of his own. Since surgeons have become conscious of the condition, however, the number of reported cases has decidedly increased. In 1928 Pemberton and Saint [4] reported nine cases observed at the Mayo Clinic in twelve years, but four years later Horton [5] was able to report from the same clinic twenty-four cases, in all of which involvement was limited to the extremities, observed in two years, which is another illustration of the fact that many supposedly rare conditions

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From the Departments of Surgery and Biochemistry of the School of Medicine of Louisiana State University, and from the Surgical Services of Charity Hospital in New Orleans.

1. Hunter, William, cited by Callander.[2]

2. Callander, C. L.: Study of Arteriovenous Fistula with an Analysis of Four Hundred and Forty-Seven Cases, Johns Hopkins Hosp. Rep. **19**:259-358, 1920.

3. Lewis, D.: Congenital Arteriovenous Fistulae, Lancet **2**:620-628 (Sept. 20); 680-686 (Sept. 27) 1930.

4. Pemberton, J. deJ., and Saint, J. H.: Congenital Arteriovenous Communications, Surg., Gynec. & Obst. **46**:470-483 (April) 1928.

5. Horton, B. T.: Hemihypertrophy of Extremities Associated with Congenital Arteriovenous Fistula, J. A. M. A. **98**:373-379 (Jan. 30) 1932.

become frequent if they are diligently sought for. In the last year we have observed seven cases, the reports of which are appended, and while we have made no effort to survey the literature, it seems reasonable to assume that a hundred or more cases are now on record.

The condition has been reported under a variety of terms, including arteriovenous fistula, abnormal pulsating venous aneurysm, arteriovenous varix, aneurysma serpentina, cirsoid aneurysm, racemose aneurysm, hemihypertrophy, angiectatic hypertrophy, aneurysm by anastomosis, pulsating angioma and simple angioma. It seems to us that the term abnormal arteriovenous anastomosis is entirely inclusive and is less likely to give rise to confusion and misconception than any of the specialized terms listed.

DIAGNOSTIC CRITERIA

Before proceeding to the point of this paper, which is to report the seven cases personally observed and to emphasize certain diagnostic criteria employed in them, a few facts concerning congenital abnormal arteriovenous anastomoses may be briefly stated.

The condition is common to both sexes though perhaps it is slightly more frequent in males. It may develop or, more properly, may come to observation, at any age (as in the man 60 years old mentioned by Horton and the woman 71 years old observed by us), but it is more likely to attract attention in early life, particularly in childhood. The most common site of occurrence is the head and neck, and the next is the extremities, which was the site in all of Horton's and in our own cases. In contrast to traumatic abnormal communications, which are practically always single, the congenital type is practically always multiple, Reid's [6] case and one of our own seeming to be the only instances on record of single congenital arteriovenous communication.

The fundamental pathologic process, as Horton pointed out, is the same whatever the location, namely, a direct communication between the artery and the vein, without the intervention of the capillary bed, which is the normal channel of communication. The gross appearance, he stated, is best studied in the intracranial variety described by Dandy, in which the veins are free from accessory coverings and it is possible to see the pulsating red arterial blood flowing against a background of dark venous blood.

Obviously, the larger the fistula and the longer its duration, the more widespread will be the local pathologic process and the more marked the systemic reaction. Halsted, Matas, Reid, Holman and others have studied these pathologic changes in detail, and a rehearsal

6. Reid, M. R.: Studies on Abnormal Arteriovenous Communications, Acquired and Congenital: I. Report of a Series of Cases, Arch. Surg. **10**:601-638 (March) 1925.

of their observations is not indicated in a communication of this purpose. It should be emphasized, however, for the point is constantly forgotten and the diagnosis is therefore many times missed, that abnormal communications between small vessels, even though they are multiple, are unlikely to produce the marked symptoms and the marked pathologic changes which even single communications between large vessels can bring about. When large vessels are involved, thrills and bruits are present, cardiac hypertrophy develops and ulcers are frequent, while spontaneous gangrene may be the end-result. When small vessels are involved, the veins in the course of years may become larger, elongated and tortuous, but thrills and bruits are likely to be absent, cardiac hypertrophy is not likely to develop and the most notable changes are likely to be the development of varicosities, ulcerations and perhaps hemihypertrophy.

The explanation of congenital arteriovenous communications, except in the briefest fashion, is again not relevant to this paper. The underlying principle, as stated by Sabin [7] and by Woollard [8] and based on their studies of the forelimb bud of the pig embryo, is that the common capillary plexus on which both arteries and veins develop is the basis for the persistence of a direct communication between the two systems. Both arteries and veins arise through differentiation from a common capillary plexus, and Sabin has shown that certain embryologic vessels may function as arteries at one stage of embryologic life and as veins at another, while Woollard has demonstrated the multitudinous communications present between the artery and the vein at the beginning of the process of differentiation. Rienhoff,[9] after personal observation of an experimentally developed fistula in the process of development, stated it as his personal view that the congenital type of abnormal vascular communication occurs as the result of persistence of the vessels or communications of the primary anlage, which, failing to develop into the normal definitive vascular tree, form anastomotic channels either directly or indirectly between otherwise normally developed arterial and venous trunks. The hundreds of such communications frequently noted, as in case 1 of our own series, seem to support this theory. Reid [10] is correct in his observation that in view of the common bed

7. Sabin, F. R.: Origin and Development of the Primitive Vessels of the Chick and of the Pig, Contrib. Embryol. **6-7**:61, 1917-1918.

8. Woollard, H. H.: The Development of the Principal Arterial Stems in the Forelimb of the Pig, Contrib. Embryol. **14**:139, 1922.

9. Rienhoff, W. F.: Congenital Arteriovenous Fistula, Bull. Johns Hopkins Hosp. **35**:271-284, 1924.

10. Reid, M. R.: Arteriovenous Communications, Acquired and Congenital: II. Origin and Nature of Arteriovenous Aneurysms, Cirsoid Aneurysms, and Simple Angiomas, Arch. Surg. **10**:997-1009 (May) 1925.

of development of each side of the vascular tree and the enormous constructive as well as destructive changes necessary before the final pattern is reached, it is a marvel not that congenital abnormal communications occasionally occur but that they do not occur more often.

That the condition is not often considered as a diagnostic possibility, chiefly, we would say, because the available methods for diagnosis are not employed, is shown by the fact that of the twenty-three cases personally reported by Horton from the Mayo Clinic, in only one was the condition recognized prior to the patient's admission. Undoubtedly many cases have been overlooked in all clinics, while in others the disease has been diagnosed as varicose veins or ulcers, trophic ulcers, thrombophlebitis, arthritis—often an associated condition—elephantiasis or peripheral vascular disease, and treatment accordingly given. It is not sufficiently emphasized in textbooks and other communications that thrills and bruits, while pathognomonic of the condition when they are present, are absent in many, indeed we would say in most, cases, particularly when only small vessels are involved. They were present in only fifteen of the twenty-three cases reported by Horton and in only one of the seven reported by us, and Horton observed that it is no more sensible to wait for their development to diagnose this condition than it would be to wait for the development of an epigastric mass to make the diagnosis of gastric carcinoma.

The first principle of diagnosis is a careful history. We have made it a routine practice in our clinic for the treatment of varicose veins to question all patients closely concerning the onset of their varicosities, the location of the first noted and the possible etiologic factors involved. Cases of varicose veins which follow such diseases or states as thrombophlebitis, infections of various sorts, surgical incisions and repeated pregnancies rarely need further consideration from this standpoint. The group of cases, on the other hand, in which the varicosities present early in life, without obvious cause, in which they are unilateral and in unusual locations and in which they are associated with ulceration, arthritic changes and hemihypertrophy, need further consideration, though again only a small number of them will prove to be true abnormal arteriovenous communications.

The small number of cases which fall into this group should be studied in three ways: by gross comparative examination of specimens of blood from the normal and from the affected extremity, by the oxygen saturation test and by arteriography. It is interesting to observe that the last two methods of diagnosis as applied to arteriovenous fistula were first used at the Mayo Clinic, whence so much of value has emerged. The oxygen saturation test was first used by the

late G. E. Brown,[11] of that clinic, in 1927 and was extended to the deeper veins by Horton in 1932. Failure to use this modification, it might be noted, is responsible for the missing of the diagnosis in many cases in which study of superficial veins does not yield the desired information. The first arteriovenous fistula to be diagnosed by arteriographic methods was reported by Horton[12] in 1933 and was of traumatic origin. In May 1935 Horton and Ghormley[13] published a report of two cases of congenital origin in which the condition was diagnosed by the same method. Arteriography for arteriovenous fistula has also been used and reported by Yater and White.[14]

The first step in diagnosis is the withdrawal of specimens of blood from the veins of the normal and the affected extremities. As a rule, unless the abnormal anastomosis is very small and deep, the blood from the affected extremity is the usual bright red arterial blood, while that from the normal extremity is the normal dark blue venous blood. In one of our own cases (7) it was the accidental observation that the color of the blood from the right basilic vein was different from that from the left basilic vein which led to the discovery of the condition.

To Horton's and Brown's oxygen saturation test we have added another modification, the study of individual samples of blood withdrawn at various levels of the affected extremity, which is divided into segments by the use of tourniquets. This method reveals the exact location of the anastomosis and, further, is of decided value in those cases in which the anastomosis is not sufficiently extensive to change the character of the blood throughout the limb and in which the diagnosis may be missed because the specimen of blood is taken from an area too remote from it to be affected by it.

The patient is placed at rest, in the prone position and with the leg elevated, for a sufficiently long time for the blood to drain completely out of the veins. Then, while the leg is still elevated, tourniquets are applied, dividing it into as many segments as may be desired, after which the patient stands until the superficial veins and varicosities are filled with blood. At this time samples of blood are withdrawn from various levels and are compared with similar specimens from the normal extremity.

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11. Brown, cited by Horton.[5]

12. Horton, B. T.: Arteriovenous Fistula Involving the Common Femoral Artery Identified by Arteriography, Am. J. M. Sc. **187**:649-652 (May) 1934.

13. Horton, B. T., and Ghormley, R. K.: Congenital Arteriovenous Fistulae of the Extremities Visualized by Arteriography, Surg., Gynec. & Obst. **60**:978-983 (May) 1935.

14. Yater, W. M., and White, C. S.: Roentgenographic Demonstration of an Arteriovenous Aneurysm by Means of Thorotrast, Am. J. M. Sc. **186**:493-495 (Oct.) 1933.

In case 1 (fig. 1) of our own series the use of this method immediately revealed the widespread character of the abnormality, and case 2 (fig. 2) furnishes another excellent illustration of the variation of the oxygen saturation of the blood adjacent to and remote from the anastomosis. Before the tourniquets were applied, blood withdrawn from the popliteal vein showed an oxygen saturation of 52 per cent and blood from the varicosities an oxygen saturation of 55 per cent, which is not a notable difference. After ligation of the saphenous vein, and again without the tourniquets, the oxygen saturation of the popliteal blood

Fig. 1 (case 1).—Comparison of the oxygen saturation of the blood of the superficial veins of the extremity exhibiting hemihypertrophy with the oxygen saturation of the blood of the popliteal vein of the opposite normal extremity.

was 53 per cent, but in the varicosities it had increased to 77 per cent. Tourniquets were then placed at the middle third of the thigh and the upper and middle thirds of the leg, each segment thus being isolated, so that since there could be no backflow from above and no filling from below it it necessarily filled only from its immediate tributaries. The oxygen saturation of the popliteal vein remained at 52 per cent, and the specimen from the lower segment showed the same percentage, but the specimen from the varicosity of the middle segment, where arteriography had already shown the abnormal anastomosis to be located, was now 84 per cent.

The samples of blood were collected under oil, and the oxygen contents and capacities were determined immediately according to the method of Peters and Van Slyke.[15] Since there is no set normal for the oxygen saturation of venous blood, the value of the test depends not on absolute standards but on a comparison of the oxygen saturation of blood from the vein studied with similar specimens from veins of the opposite extremity or veins at other levels of the same extremity.

By means of arteriography, as Horton pointed out in his original communication and as we have proved conclusively in the seven cases we have personally observed, it is now possible to locate the supposed

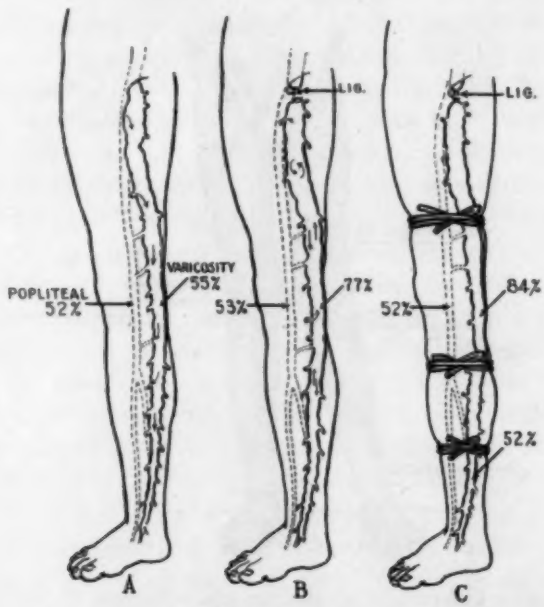

Fig. 2 (case 2).—Demonstration of the value of the tourniquet in the localization of the site of the abnormal anastomosis by means of the oxygen saturation test. *A* shows the percentage of oxygen saturation before ligation of the saphenous vein or application of the tourniquet; *B*, the percentage of oxygen saturation after ligation of the saphenous vein at the saphenofemoral junction, and *C*, the percentage of oxygen saturation after the application of tourniquets, showing that the abnormal arteriovenous anastomosis is located about the knee.

anastomosis with absolute accuracy as well as merely to confirm its existence. Injection of the vascular system with stabilized solution of colloidal thorium di-oxide as has been proved in the last three years and

15. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

in several hundred cases,[16] is a simple, efficacious, harmless method of demonstrating the state of the vascular tree, and in this type of pathologic change it is particularly valuable in that it demonstrates as no other method can the exact site of the abnormal communication, its size and the number and extent of the vessels involved.

The arteriograms, it should be emphasized, are not always easy to interpret. When the anastomosis is between large vessels there is naturally no difficulty. When smaller vessels are involved, however, repeated observations may be necessary, and it is essential that the plates be read by a person thoroughly conversant with the appearance of the normal vascular tree when it is visualized by this method, for only by comparison with normal standards can one detect abnormalities involving the small arteries and veins.

It would be highly improper, of course, to propose a classification based on only seven cases, but at that it is interesting to observe that in this small series certain definite types of anastomosis are noted, of which type *B* is the most frequent. The highly magnified schematic drawings which illustrate these various types (fig. 3) were made directly from the arteriograms of these patients and may be described as follows:

Type *A*. The normal distribution of the arterial system in the region of the knee. The terminations of the small arteries are to be noted particularly.

Type *B*. A multiple type of communication which we have chosen to designate as arteriolar-venous. It involves only the more superficially placed smaller vessels. It is not inconceivable, we suggest, that this type of anastomosis is akin to the vascular nevus or "port wine" birth mark which occurs on the surface of the skin, and we hope at some future date to be able to study the latter condition by arteriography and attempt to verify our surmise.

Type *C*. A combination of two types of abnormal arteriovenous anastomosis. In addition to the variety already described as type *B*, there is present also the single anastomosis between a large artery and a vein (*c*), usually seen in the traumatic variety of abnormal arteriovenous communication. The upward path of the vein and its communication with the large varicosity (*d*) should be noted.

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16. Veal, J. R., and McFetridge, E. M.: Technical Considerations in Arteriography of Extremities with Thorotrast, Am. J. Roentgenol. **32**:64-71 (July) 1934; Arteriography in Gangrene of Extremities by Use of Thorium Dioxide (Thorotrast): Study Based on Twenty-Seven Cases, Ann. Surg. **101**:766-775 (Feb.) 1935; Adequate Circulation in Extremities: Arteriography as Test for Determining Limits; Preliminary Report Based on Thirty Amputations, J. A. M. A. **104**:542-545 (Feb. 16) 1935.

Type *D*. A type of communication between a digital artery (*a*) normal in size, shape and distribution and normal veins (*b*) by way of small arterioles or vascular pockets which resemble small tumors. This type of communication, we suggest, may finally develop into the true angiomatous type.

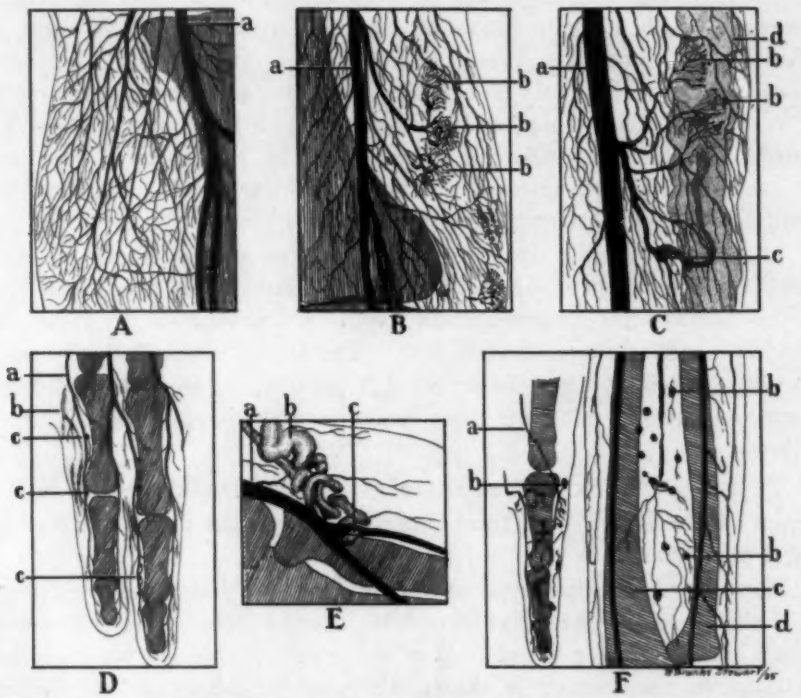

Fig. 3.—Schematic drawings made under magnification from arteriograms. *A* shows the normal distribution of the arterial system about the knee, *a* indicating the popliteal artery. Note the gradual branching and visualization of the fine arterioles. *B* shows an arteriovenous anastomosis just above the knee (case 1). The lower femoral artery is indicated by *a* and the dilated arterioles and small arteries at their terminations, just before entering the venous channels, by *b*. *C* shows an arteriovenous anastomosis which is a combination of two types (case 4). The femoral artery is indicated by *a*, dilatation of arterioles at their junction with the vein by *b* and single anastomoses between a large artery and a vein by *c*. Note that this vein also empties into the large varicosity shown in *d*, which is an example of the direct emptying of all the anastomoses into the large superficial varicosity. *D* shows an angiomatous type of anastomosis (case 7). Note the normal size and distribution of the digital vessels and the small vascular tumors through which the arteries empty directly into the venous circulation without an intervening capillary circulation. *E* shows a large single anastomosis between a vein and an artery just distal to the origin of the radial artery (case 3). *F* shows a section from an arteriogram of the lower part of the forearm and little finger (case 5) which demonstrates the formation of tufts of small arteries from arterioles. Note the direct communication between these arterial tufts and the venous circulation, without the intervention of a capillary circulation.

Type *E*. A direct single communication between a large artery and vein (*c*) arising in dilated varicosities. This type of anastomosis, as has been pointed out, is the type usually seen in the acquired form but is not usual in the congenital form. The proximal dilatation of the artery, to which Halsted was the first to call attention, is well shown here in the radial artery.

Type *F*. The angiomatous, or vascular tumor, type of communication. The digital artery (*a*) gives rise to numerous tufts of small arterioles which form vascular tumors. The same type of communication is noted throughout the lower half of the forearm.

In the seven cases, then, there are five distinct types of abnormal arteriovenous communication, three cases (1, 2 and 6) being instances of the arteriolar-venous, or *B*, type and the same type of anastomosis also appearing in association with another variety in case 4. Clearly this is the most usual type. It will be of interest to study additional cases, however, according to this classification, to determine whether the other types seen in this small group are accidental departures from a standard pattern or actually represent other varieties of anastomosis.

TREATMENT

The treatment of traumatic or acquired arteriovenous fistula is usually a fairly simple matter, since the communication is usually single and, as Pemberton pointed out, involves large vessels accessible to surgical approach; the problem, therefore, is limited to checking the arterial leak without interference with the blood supply of the tissues, and the abundant collateral circulation usually obliterates the risk of gangrene. The treatment of congenital abnormal communications, however, is another matter, since the connecting channels are practically always multiple and are frequently so small that direct surgical attack is difficult if not impossible. The ideal treatment, extirpation of the offending anastomosis, for obvious reasons is rarely possible. Ligation of the artery alone does little good in most cases and may do considerable harm. In seven of the thirty-four cases reported by Lewis, for instance, ligation of the artery had to be followed by amputation because of the development of gangrene. There is less risk if the vein is ligated also, but as a rule ligation proximal to the fistula serves merely to diminish the amount of blood flowing through it, the proportionate distribution being little changed and the diminished flow actually being detrimental, if anything.

The value of arteriography as a method of determining therapy in arteriovenous fistulas was pointed out by Horton in his first report, and we have found it of great value, especially in combination with the Perthes test of the deep circulation. Horton also mentioned its value

as a posttherapeutic measure, to check what has been achieved by the treatment adopted.

In our own cases, for instance, we were able to determine that in case 3, in which the communication was apparently single (fig. 4), simple ligation of the anastomosis would be sufficient, and we regret that the patient's refusal to consider surgical treatment made the test of our position impossible. In case 1 the widespread character of the anastomoses, as demonstrated by arteriography, showed that any surgical measure short of amputation, which was not then indicated, would be useless. In cases 1, 4 and 6, in which arteriography demonstrated

Fig. 4 (case 3).—Arteriogram showing an arteriovenous fistula arising from the radial artery. Note the single communication and the tortuous and dilated veins.

the superficial character of the anastomoses and the Perthes test showed the deep circulation to be adequate, the use of sclerosing substances seemed as safe as it proved to be.

In case 5, that of the angioma of the hand and forearm, arteriography (fig. 5) showed that the sclerosing substance could not possibly reach all the involved vessels, and the surgeon in charge of the case thereupon decided on amputation on the basis that a process of this sort is progressive and, in a sense, malignant. It is regrettable that circumstances make amputation the only possible procedure in many

cases, which makes it conservative, as Pemberton and Saint pointed out, to be radical in early life and to treat abnormal vascular communications as soon as they are discovered, to avoid such consequences later. At what time amputation should be done, they added, in those cases in which it is necessary, depends on the patient, the site of the anastomosis, the rapidity of its development, the degree of local disability and the presence or absence of systemic changes. In the absence of cardiac changes or destruction of tissue it may be safely deferred, they concluded, until inconvenience and disability demand it.

Surgical treatment is not always a simple matter in such cases. Busche, whose case Callander cited, removed a purple, pulsating tumor

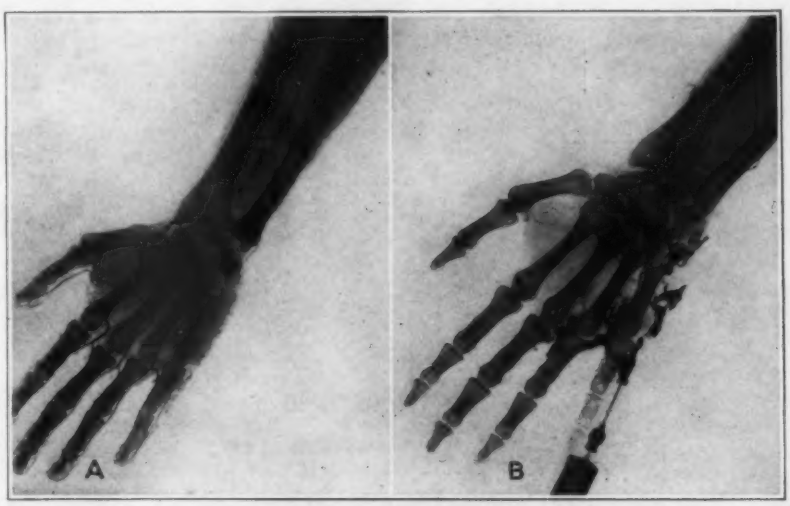

Fig. 5 (case 5).—*A*, an arteriogram of the lower part of the forearm and hand, showing the distribution of the hemangiomas. *B*, visualization of the venous tree after the injection of a stabilized solution of colloidal thorium di-oxide. Note that the angiomatous tumors fill from the venous as well as from the arterial side.

of the right temple in a young child "with a few quickly executed sweeps of the scalpel." But cauterization of the wound and finally ligation of the external carotid artery were necessary to control the hemorrhage which persisted from the whole raw surface. Bernheim [17] reported another case of arteriovenous fistula of the first part of the brachial artery and vein in which amputation, prepared for with the utmost care, was followed by a terrific, exsanguinating, almost fatal, hemorrhage.

17. Bernheim, B. M.: Congenital Arteriovenous Fistula in Left Brachial Artery and Vein with Secondary Arterial Blood Supply to Arm, Ann. Surg. **81:** 465-469 (Feb.) 1925.

The number of cases in which treatment was obviously needed but was not given, probably because the choice seemed to lie between no treatment and amputation, is as surprising in the reported series as is the paucity of reported cures. The three patients in our own small series who were treated by the simple injection of a sclerosing substance, in one case after ligation of the saphenous vein, have remained well to date, though it is too early, of course, to say that the cure will be permanent.

REPORT OF CASES

CASE 1.—A Negro girl aged 13 first observed at 6 years of age that her right leg was longer and larger than her left (fig. 6). Undoubtedly her attention was attracted to the abnormality by the fact that at the same time a dull, aching pain

Fig. 6 (case 1).—Hemihypertrophy and superficial varicosities. Note the uniform enlargement of the involved extremity and the absence of any trophic disturbance.

developed in the same leg, which was more severe in the knee and foot, which had persisted since and which was aggravated in the muscles of the calf by full extension of the extremity. Her history was otherwise without incident.

Except for this condition and an associated enlargement of the right labium majus, the physical examination gave essentially negative results. The right labium majus was almost twice the size of the left but exhibited no dilated vessels or other abnormalities which might account for the enlargement. The child had a typical scoliosis and walked with a definite limp. The right saphenous vein was grossly enlarged, but no trophic disturbances were present and no edema. There was no thrill or bruit at any level. From the anterior superior spine of the

ilium to the tip of the internal malleolus the right leg measured 79 cm. and the left 74.5 cm. From the anterior superior spine of the ilium to the tip of the patella the right leg measured 39 cm. and the left 37 cm. The circumference of the right leg was from 1 to 2 cm. larger than the left, depending on the level at which the measurements were taken, and the toes on that side were slightly (0.25 cm.) longer than the toes on the left foot.

The Wassermann reaction was negative. The blood count showed marked secondary anemia (3,630,000 red cells with a hemoglobin content of 80 per cent). The blood chemistry was within the normal range, and the basal metabolic rate was minus 9. A flat plate of the heart, supplemented by electrocardiographic study, revealed no abnormalities. Roentgenographic study of both extremities showed the bones of the right leg to be uniformly longer and larger than those of the left.

Tourniquets were applied to the right leg above the knee, at the middle of the leg and about the ankle, and specimens of blood were secured from each of the three segments. All of them were bright red, in contrast to the bluish blood from the left popliteal vein, from which it was secured in the absence of dilated superficial veins. The specimen from the left leg showed an oxygen saturation of 28 per cent against 86 per cent for the specimen from the right thigh and 88 per cent for the specimens from the middle of the leg and the lower segment.

The absence of bruits and thrills suggested that if an abnormal arteriovenous communication should be present, as the hemihypertrophy would seem to indicate, only small vessels were involved. The uniformly high oxygen saturation again suggested that the anastomoses were probably multiple and probably involved the entire leg. Arteriography with a stabilized solution of colloidal thorium di-oxide confirmed both these surmises. Although the femoral and popliteal arteries and the larger superficial branches were entirely normal, the smaller, more superficial arteries were markedly dilated. Furthermore, throughout the entire area visualized, namely, from the lower half of the thigh to the foot, these vessels emptied directly into the venous channels, literally by the hundreds. A second exposure, ten seconds later, revealed what is best described as a sort of snowbank mottling of the opaque material throughout the entire leg and the lower part of the thigh.

These findings are in direct contrast to the findings in normal persons. When the vascular supply is normal, an arteriogram taken immediately after the injection of the opaque substance shows it filling not only the larger arteries but also the small arterial vessels, in which it apparently terminates. A second picture, made from six to ten seconds later, shows it in the veins, large and small alike, including the popliteal vein. Both the course and the contour of the vascular tree are smooth and even, and the distribution is according to a more or less definite pattern.

In this case there were multiple abnormal anastomoses between the arterioles and the venules of the involved extremity (type B), none of the larger or medium-sized arteries being affected but all of the smaller vessels, both superficial and deep, taking part in the anomaly. Some anomaly of the popliteal vein was apparently present also, for it was not visualized, nor could it be located with the exploring needle.

Because of the widespread character of the anastomosis, plus the fact that the patient's pain was markedly increased when she was made to walk with the tourniquets in place, it was felt that injection of some sclerosing substance into the superficial veins was contraindicated and would, in addition, be of no value. Indeed, the character of the anastomosis seemed to preclude any treatment for the

present, though amputation may be necessary later. The child was accordingly discharged, after intensive treatment of the secondary anemia, with instructions to return at regular intervals for observation.

CASE 2.—A white man aged 36 applied to the Charity Hospital for the treatment of large varicosities of the lower part of the right thigh and the upper part of the leg. They had been noted for the first time about the twentieth year of life and had gradually increased in size. Pain had been associated with them for a number of years and recently had been so severe that the patient was almost incapacitated. The extremities were equal in size and length, and no trophic disturbances were noted. Perthes' test of the deep circulation gave negative results. No bruit or thrill was present in the standing position, but the early onset, the large size and the unilateral character of the varicosities suggested the diagnosis of an abnormal arteriovenous communication, and the patient was therefore studied from this standpoint.

Arteriography showed a normal circulation in the lower two thirds of the right leg. In the upper third of the leg and the lower third of the thigh were noted frequent abnormal communications between the smaller arteries and the varicosities described, the anomalous channels being considerably more numerous just above the knee (type *B*).

The oxygen saturation test, without the use of tourniquets, showed an oxygen saturation of 52 per cent in the blood from the right popliteal vein and of 55 per cent in blood from the varicosities at the level of the right knee. After ligation of the saphenous vein at the saphenofemoral junction, the oxygen saturation of the blood from the varicosities was 77 per cent and of the blood from the popliteal vein, 53 per cent. When tourniquets were applied at the middle of the leg and just above the knee, there was no change in the oxygen saturation of the popliteal vein, and blood from the lower segment of the leg, at the ankle, showed almost the same percentage, 55 per cent, but blood from the thigh, between the upper and the middle tourniquets, showed oxygen saturation of 84 per cent, which proved conclusively that the abnormal anastomosis involved only this area.

Under treatment with repeated injections of sodium morrhuate there was prompt thrombosis of the varicosities, and the patient was relieved from his symptoms. He has remained well for nine months, and repeated examination of the involved area has shown no tendency to recurrence of the varicosities.

CASE 3.—A Negro man aged 32 was admitted to the Charity Hospital for the treatment of gastro-enteritis. In the course of routine examination large varicosities were noted in the left antecubital space. Careful questioning revealed the fact that they had existed since early childhood, perhaps from birth, and had gradually increased in size. There was no difference in the size or length of the arms, and the patient, who was a laborer, had observed no weakness or other abnormality of the affected arm.

The radial pulse was the same in the two arms, as was the blood pressure above the elbow, and no trophic disturbances were noted. Roentgenographic study showed no changes in the bones. A distinct thrill could be felt over the varicosities on palpation, and a loud bruit was noted on auscultation, which disappeared when the brachial artery was compressed.

The oxygen saturation of blood from the left antecubital space was 81 per cent, against 21 per cent for a similar specimen from the right arm. Arteriography (fig. 4) showed a single large, direct communication between the upper end of the radial artery and the superficial varicosities in the antecubital space (type *E*), and repeated study failed to reveal any other.

Undoubtedly the trouble could have been corrected by simple ligation of the vein involved, with excision of the varicosities, but the patient, in the absence of more annoying symptoms, refused treatment. Perhaps, too, operation would not have been as simple as it seemed, for in the similar case reported by Reid, which seems to be the only other one on record of a single congenital anastomosis, two operations were necessary and ten ligatures had to be applied on the various vessels directly or indirectly involved.

CASE 4.—A white woman aged 71, who was admitted to the hospital with a diagnosis of sciatica, complained of pain extending from the posterior aspect of the left thigh to the foot. It had been present for eleven years and was aggravated by standing and walking. The only point of interest in the physical examination was the presence of large varicosities extending from the left buttocks down to the posterior aspect of the thigh, where they united with the saphenous vein and continued down to the foot. They were first noted on the posterior aspect of the upper part of the thigh when the patient was about 18 years of age and had gradually increased in size and extent. Pain had developed eleven years before admission to the hospital. The early onset of the varicosities in such an unusual location naturally suggested the diagnosis of an abnormal arteriovenous anastomosis, and the patient was therefore studied from this standpoint.

Tourniquets were applied according to the method described, and blood was drawn at various levels. The specimens taken from the two segments above the knee were bright red, and those from the segments below the knee were typical dark venous blood.

Arteriography revealed many fine direct communications between the small arteries of the thigh and the varicosities described, with one direct anastomosis between a large muscular artery and a vein near the middle of the thigh, the vein becoming progressively larger and more dilated as it approached the varicosities. Beyond the anastomosis the vein turned upward and outward, emptying into the varicosities at the area in which the small abnormal anastomoses were located. This type of abnormal communication (*C*) actually is a combination of two other types, one between a large artery and vein (*E*) and the other between the arterioles and the venules near the skin (*B*). As far as could be judged from the single plate, all the dilated veins which were part of the abnormal anastomosis terminated in the upper 4 inches (10 cm.) of the varicosities.

The patient was treated by ligation (in two places) of the varicose veins, followed by repeated injections of sodium morrhuate. Satisfactory thrombosis followed, and the pain rapidly disappeared.

CASE 5.—A white man aged 24 was admitted to the service of Dr. Isidore Cohn in the Charity Hospital. Dr. Cohn requested us to make arteriographic studies, and the case is reported by his permission.

The patient complained of a dull aching pain in the middle third of the right forearm, which had developed fifteen days before admission and which was associated with a swelling of the forearm and hand. He stated that as long as he could remember small tumors composed of dilated veins had been present in this hand and arm. Physical examination revealed the masses described, which decreased in size when the extremity was elevated. Large, dilated veins coursed over the lateral posterior portion of the lower part of the forearm and the upper third of the hand, and bluish purple areas were observed on the palmar surface of the hand in the hypothenar region. The blood pressure was 100 systolic and 70 diastolic in each arm. There was no evidence of increased heat in the hand

and arm, and no trophic disturbances were present. The upper extremities were alike in size, length and function.

A flat plate of the right forearm and hand revealed atrophic changes in the fourth and fifth metacarpal bones and in the bones of the little finger. Thickening and induration of the soft tissues of the hypothenar region were also noted. Arteriography (fig. 5) with a stabilized solution of colloidal thorium di-oxide showed direct arteriovenous communication (type F) in many areas of the lower part of the forearm, the ulnar side of the hand and the small and ring fingers. The tiny arterioles were grouped in circular, tuftlike whirls, and the opaque substance passed rapidly from them into the veins. The interpretation of the arteriogram was that there were numerous vascular tumors along the lower part of the forearm and the ulnar side of the hand.

An unsuccessful attempt at ligation of the involved vessels was followed by amputation through the lower third of the humerus. The pathologist's report on the amputated specimen reads as follows:

On section there were seen numerous dilated and tortuous thin-walled vessels filled with blood clot, which were located in the extensor muscles, the digitorum longis muscle and similar structures. They extended down into the wrist, where they were located in the fascia and were closely adherent to the extensor tendons and terminated in the tip of the little finger. There was no involvement of the anterior surface of the forearm or hand. The diagnosis based on the microscopic picture was hemangioma.

CASE 6.—A Negro man aged 37 applied to the Charity Hospital for treatment of a large mass of tortuous and dilated varicosities located over the upper half of the posterior aspect of the right leg. They had first been observed at the age of 12 years and had gradually increased in size. The only symptom was a dull localized pain, which came on after the patient stood for a long time. There was no thrill or bruit, but when the limb was elevated the veins did not empty completely, as the usual type of varicose vein does.

The involved portion of the leg was divided into three segments by the application of tourniquets, and samples of blood were removed from each. All three specimens were bright red, and each showed oxygen saturation of approximately 90 per cent. Arteriography (fig. 7) showed multiple anastomoses between the arterioles and the venules (type *B*). Since the Perthes test of the deep circulation gave negative results, the use of injections of sodium morrhuate to produce sclerosis of the affected veins was considered safe, and under this treatment the patient has shown both objective and subjective improvement.

CASE 7.—A white man aged 23, a medical student, was undergoing routine tests when it was observed by one of us (W. M. McC.) that the blood withdrawn from his left basilic vein was unusually bright, whereas that from the right vein was the normal dark blue of venous blood. Examination showed the right arm to be slightly and uniformly larger than the left; there were no abnormalities of any sort in the left arm. There were no symptoms of any sort, and except for the accidental observation of the difference in the color of the blood from his arms, the condition would not have been discovered.

Examination of a specimen of blood from the left basilic vein, without the application of tourniquets, revealed the oxygen saturation to be 85 per cent, against 65 per cent for the specimen from the right side. Three arteriograms were made after the injection of a stabilized solution of colloid thorium di-oxide. The first exposure, made immediately after the injection, showed the opaque substance filling the arteries of the hand and the proximal half of each finger in

the normal manner. A second exposure, two seconds later, showed a completely changed picture. At this time all the digital arteries were visualized, and fifteen or twenty small dilated vessels were seen leading from the small arteries into the soft tissues. They were about the size of a pinhead, and their distribution was irregular; four or five were in the pulp of the thumb, and the others were located along the lateral margins of the finger. A third arteriogram, made six seconds after the second one, showed these dilated vascular pockets emptying directly into the venous circulation, with no evidence of a capillary circulation.

Fig. 7 (case 6).—Congenital arteriolar-venous anastomosis in the region of the right knee. Note the dilated, tortuous vessels and their distribution. The oxygen saturation of the venous blood from this region was 92 per cent, but no thrill or bruit was noted.

This type of anastomosis (*D*), while it is the most unusual of the whole series, undoubtedly is more frequent than is suspected, since it is probably, as in this case, discovered only by accident. This subject was not treated, in the absence of symptoms, and will probably never suffer from his abnormality, although he will be carefully followed to determine whether the condition is progressive. It may, of course, be an early manifestation of the hemangiomatous type of anastomosis (*F*).

SUMMARY

Abnormal arteriovenous anastomoses of the extremities, especially small ones, are undoubtedly more common than is generally realized.

The congenital type, which has a true embryologic origin, on the basis of the derivation of each side of the vascular tree from a common bed, most often has multiple communications, in contrast to the usual single communication of the acquired type.

Such abnormal communications should be suspected in all cases of varicosities, particularly of the unilateral type, which appear early in life and in unusual locations. They should also be suspected in cases of chronic ulcers of the leg in young subjects without obvious cause, in cases of hemihypertrophy and in cases in which there are trophic disturbances of the extremity of obscure etiology.

The oxygen saturation test is an exceedingly useful diagnostic measure, the value of which is enhanced by the study of specimens of blood withdrawn between tourniquets, as suggested in this paper, which definitely locates the anastomosis by permitting the maximal concentration of arterial blood in the superficial veins.

The value of arteriography should also be emphasized, for there is no other method of demonstrating the exact site, type, number, size and distribution of the abnormal anastomoses.

A possible classification of abnormal anastomoses is suggested on the basis of the arteriographic findings in these few cases.

By use of arteriography it is possible to determine which patients should be treated by surgical measures, which can safely be treated by the injection of sclerosing substances if the Perthes test demonstrates the adequacy of the deep circulation and which must be left untreated unless and until amputation proves necessary.

Seven cases of congenital abnormal arteriovenous anastomoses are reported.

CRANIAL VENOUS SINUSES

CORRELATION BETWEEN SKULL MARKINGS AND ROENTGENOGRAMS OF THE OCCIPITAL BONE

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AND
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In a previous communication [1] one of us (B. W.) has described the normal anatomic variations in the cranial venous sinus patterns, particularly in the region of the torcular Herophili. As a part of that study, it was noted that the markings on the occipital bone closely corresponded to the differences in the volume of the lateral sinuses and followed exactly the distribution of these sinuses. To recapitulate, 47 of 100 roentgenograms of the skull showed equal markings, 32 demonstrated a noticeable difference in size, 15 showed indefinite markings on each side, 2 showed no bony evidence of the sinus pattern on either side and 4 showed no markings on one side and very definite markings on the opposite side. For practical purposes, discussed later, it is important to have a similar clinical record of these observations, and it is the purpose of this paper to correlate roentgenograms of this portion of the skull with the anatomic records already made.

Except for isolated instances, there are few reports in the literature pertaining to this subject. The most interesting of these is that of Ersner and Myers.[2] They discussed roentgenographic evidence secured in the course of the study of 4 cases of disease of the middle ear associated with thrombosis of the lateral sinus. The roentgenograms in the first case suggested absence of the right lateral sinus and dilation of the left lateral sinus, a finding that was substantiated at operation; those in the second case, one of sinus thrombosis involving the right side, revealed a larger left lateral sinus; those in the third case, one of sinus thrombosis on the right side, demonstrated a larger right lateral sinus; the roentgenogram in the fourth case, one of petrositis on the right

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From the Departments of Surgery and Roentgenology, Johns Hopkins Hospital.

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side, showed a larger left jugular foramen. Wanamaker [3] reported an instance of variation in the sinuses demonstrated roentgenographically; in this case the left lateral sinus was the smaller. Campbell [4] recommended the use of the roentgenogram to diagnose anatomic variations in the two lateral sinuses, but he did not pursue the subject in detail. Berg and Constans [5] studied the roentgenographic picture in 158 cases of mastoiditis prior to operation, paying particular attention to the location of the sinus plate in relation to the mastoid cells. In 11 cases the roentgenograms showed absence of the lateral sinus on one side; in 4 of these cases the absence was noted on the diseased side. Both Frenckner [6] and Dixon [7] have experimented with the injection of opaque mediums into the cranial venous sinus system, the former using monkeys and human cadavers and the latter dogs and in a few instances human clinical material. Their efforts, although highly laudable, have not as yet brought forth a controlled series of cases from which normal variations in the sinus pattern may be ascertained. Finally, Moniz and his associates [8] have endeavored to picture the venous drainage of the brain in the course of arterial encephalography. Their plates, taken in a lateral plane from four to fifteen seconds after the intracarotid injection of 15 cc. of colloidal thorium dioxide, present an effective understanding of the patency of the sinuses. No study, however, of the normal venous patterns has been made.

The literature describing the relationship between the volume of the sinuses and the markings on the skull has already been extensively reviewed and confirmed personally. Little has been added since the classic work of Le Double,[9] whose conclusions may be quoted with profit.

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8. Moniz, E.; Alves, A., and de Almeida, F.: La visibilité de sinus de la dure-mère, par l'épreuve encéphalographique, Presse méd. **40**:1499-1502, 1932.

9. Le Double, A.-F.: Traité des variations des os du crâne de l'homme et de leur signification au point de vue de l'anthropologie zoologique, Paris, Vigot Frères, 1903.

The study of the variations in the posterior venous sinuses of the dura mater is quite favorable to the thesis that the primitive venous system of the brain is bilateral and symmetrical in origin. The greatest part of the variations in these sinuses consist, in reality, in their bilateral nature, their separation by a septum, continuous or interrupted, and of a varying length (gun barrel sinus), and lastly by their early or late bifurcation. This said, it is easy to explain the variations in the markings on the internal surface of the occipital bone; they correspond to the volume of the venous sinuses that they contain. Is it not an accepted fact that every vessel of consequence is generally indicated by a groove on the inner surface of the skull?

This study was undertaken on the first 100 satisfactory roentgenograms available in the files of the department of roentgenology of the Johns Hopkins Hospital. The plates were made of 56 males and 44 females, of whom 90 were white and 10 Negroes. There were from 14 to 23 persons in each of the first five decades of life, with only a few in the later periods of life. No attempt was made to choose specific films from a clinical or anatomic standpoint, except to rule out those which showed operative or pathologic deformities affecting the region of study. The criterion of choice was fundamentally that of selecting diagnostic films from an average technical point of view.

Since the primary interest in this work was centered in the torcular Herophili and the transverse portions of the lateral sinuses, only anteroposterior roentgenograms of the occipital bone were eligible for study, and only those were used that projected the area of the inion above the orbital margins. Since bilateral comparison was essential, only true projections of the sagittal plane of the skull perpendicular to the film were acceptable.

The occipital view only was used in this study (Whitmore,[10] Hirsch,[11] Jerman [12] and Towne [13]). This was chosen for several specific reasons in addition to the obvious one already noted. The selection of the anteroposterior view rather than the lateral stereoscopic view for the study of the lateral sinuses lessens not only the factor of human error in estimating differences but also that of technical variations that are inevitable in the latter projection. The occipital view is relatively simple to obtain, and the postural requirements are applicable to nearly any patient. Finally, as long as the primary projection criteria are observed in choosing films for study, a relatively wide range of tube-skull-film angulation is apparently permissible.

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10. Whitmore, W. H.: The Occipital View: Modified Technique, Am. J. Roentgenol. **31**:271-272, 1934.

11. Hirsch, I. S.: The Principles and Practice of Roentgenological Technique, New York, American X-Ray Publishing Company, 1920.

12. Jerman, E. O.: Modern X-Ray Technique, St. Paul, The Bruce Publishing Company, 1928.

13. Towne, E. B.: Erosion of the Petrous Bone by Acoustic Nerve Tumor, Arch. Otolaryng. **4**:515-519 (Dec.) 1926.

Fig. 1.—Anteroposterior roentgenogram showing lateral sinuses of equal volume.

Fig. 2.—Anteroposterior roentgenogram of the lateral sinuses, the right being larger than the left.

Fig. 3.—Anteroposterior roentgenogram of the lateral sinuses, the left being larger than the right.

Fig. 4.—Anteroposterior roentgenogram showing a right lateral sinus and absence of the left lateral sinus.

Fig. 5.—Anteroposterior roentgenogram showing a left lateral sinus and absence of the right lateral sinus.

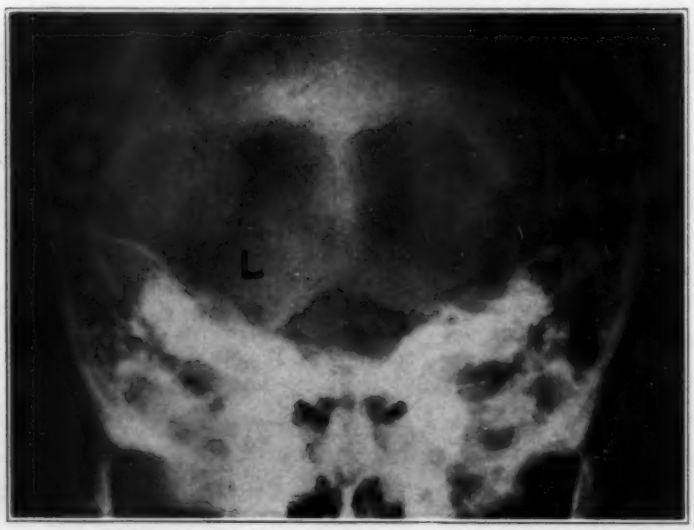

Fig. 6.—Anteroposterior roentgenogram showing absence of bony markings of the lateral sinus.

On the other hand, relatively standardized technic in any roentgenographic examination is desirable, and the selections for demonstration were, of course, chosen from an optimum group. Since most optimum technics have eventually been ascertained by the trial and error method, after due theoretical consideration, it will take further study to evolve such a method for the evaluation of the relative caliber of the lateral sinuses. This problem will be considered in detail in a later report. For the present, the observations shown in tables 1 and 2 have been made.

TABLE 1.—*Variations in the Lateral Sinuses*

Sinuses	No. of Cases	Degree of Variation	No. of Cases
Bilateral and equal	46		
Right lateral sinus greater than left	30	Slight difference	8
		Moderate difference (2:1)	15
		Pronounced difference (2:1 plus)	7
Left lateral sinus greater than right	11	Slight difference	1
		Moderate difference (2:1)	5
		Pronounced difference (2:1 plus)	5
Indistinct markings	6		
Absence of markings	3		
Left lateral sinus present; no right	1		
Right lateral sinus present; no left	3		

TABLE 2.—*Comparative Anatomic Observations on Sinuses and Skull* [1]

Sinuses	No. of Cases	Degree of Variation	No. of Cases	Skull	No. of Cases
Bilateral and equal	48				47
Right lateral sinus greater than left	38	Slight difference	23		
		Moderate difference	12		
		Pronounced difference	3	Noticeable difference	32
Left lateral sinus greater than right	10	Slight difference	5		
		Moderate difference	5		
Right lateral sinus present; no left	1			No markings on one side; marked on the opposite	4
Left lateral sinus present; no right	3				
				Indefinite markings	15

COMMENT

Clinical evidence of the relative size of the lateral sinuses secured by the use of roentgenograms of the skull is of value from two points of view. It has long been established that the Queckenstedt test, or the application of the Queckenstedt test by Tobey and Ayer, is influenced by the caliber of the efferent cranial venous channels, i. e., the lateral sinuses and the jugular veins. A smaller channel, carrying a smaller volume of venous blood, will give a lower and slower response in the spinal manometer reading on compression of that channel and vice

versa. An advanced example of this anatomic abnormality in association with a positive Queckenstedt test has recently been noted.[1] Studies to demonstrate the correlation between the response to the Queckenstedt test and the roentgenographic evidence of the volume of the lateral sinus in normal persons are now under way to elucidate this problem. The observations in this paper, then, form the basis for further demonstration of the relationship of the volume of the sinuses, the markings on the skull, the roentgenographic evidence of these bony markings and the validity of the Queckenstedt test.

Secondly, in those cases of thrombosis of the lateral sinus or of the jugular vein in which there are signs of intracranial pressure without evidence of cerebral abscess, purulent meningitis, etc., it is of clinical value to appreciate the probable volume of the main venous channels leading from the brain. In three of Ersner and Myers' cases the larger venous channel was patent, there were no signs of increased intracranial pressure and the patients survived. In 1 case there was thrombosis of the larger sinus, as portrayed in the roentgenograms of the skull, and the patient died with evidence of advanced intracranial pressure. The authors stated:

> In the cases that involved the side of the smaller sinus and jugular foramen, the pressure symptoms were practically nil, even those where X-ray revealed a suppuration of the petrous portion of the temporal bone. These symptoms were absent, due to adequate circulation. Those cases which involved the side of the larger sinus presented the neurologic signs which we recognize as being due to disturbances in venous circulation and to increased intracerebral pressure.

There are numerous other reports of back pressure phenomena in the brain, all, however, without roentgenographic evidence of sinus caliber. Those of Klestadt[14] Brinitzer,[15] Neubauer,[16] Cairns,[17] Ohnacker,[18] Uffenorde[19] and Syme[20] may be briefly noted.

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14. Klestadt, W.: Zerebrale Symptomenkomplexe bei otogener Sinusphlebitis, Ztschr. f. Laryng., Rhin., Otol. **13**:83-105, 1924.

15. Brinitzer: Hirnsymptome und Stauungspapille nach Sinusphlebitis, Klin. Wchnschr. **3**:1649, 1924.

16. Neubauer, A.: Nach acuter Mittelöhrentzündung aufgetretene Sinusthrombose mit Aphasie und Hemiplegie, Jahrb. f. Kinderh. **104**:361-364, 1934.

17. Cairns, Hugh: Abscess of the Brain, J. Laryng. & Otol. **45**:385-397, 1930.

18. Ohnacker, P.: Zirkulatorisch bedingte Hirnerscheinungen im Anschluss an Sinus-und Jugularisausschaltung, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **131**: 1-12, 1932.

19. Uffenorde, W.: Zerebrale Symptome bei unkomplizierten otogen Extraduralabszess und bei Sinus thrombose, Ztschr. f. Laryng., Rhin., Otol. **22**:151-159, 1932.

20. Syme, W. S.: Two Unusual Cases of Lateral Sinus Thrombosis, J. Laryng. & Otol. **48**:547-550, 1933.

CONCLUSIONS

A preliminary study of 100 consecutive routine roentgenograms of the occipital bones of normal persons, taken in the anteroposterior projection plane, has demonstrated relative differences and variations in the size of the bony markings of the lateral sinuses that closely correspond to the anatomic observations previously reported.

This normal standard of variation, appraised by roentgenographic study, is of clinical value in determining the significance of irregularities obtained by the Queckenstedt test and in determining the dynamics of the venous return from the brain in the presence of thrombosis of the lateral sinus or of the jugular vein.

NOTE.—The photographs presented in this paper depict anteroposterior roentgenograms of the various sinus patterns. The particular films were chosen because they offered the most favorable chance for satisfactory reproduction. Any film in this large group, however, revealed its particular type of pattern satisfactorily; not all would reproduce convincingly.

PREPARATION OF OPERATIVE FIELD

REPORT OF A SURVEY OF SEVENTEEN SURGICAL TEACHING CLINICS

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Resting with a false sense of security on the generally accepted listerian principle, the casual surgeon has not greatly concerned himself with advances in the preparation of the operative field. A large number of surgeons working in open hospitals accept this preparation as a matter of routine. The same unaltered technic may be in vogue many years without revision, until some accident, some grave infection of the wound or even a fatality will call attention to a fault in the technic. Recently Meleney,[1] from the service of the Presbyterian Hospital in New York, surveyed the cases of infection of the wound over a period of ten years and found that 12.5 per cent of the clean wounds showed some type of inflammatory reaction. In a recent symposium from the New York hospitals it was found that in about 3 per cent of all of the laparotomies there was some degree of dehiscence of the wound. Some authors were of the opinion that in most of these cases infection of the wound played a prominent rôle.

When one attempts to guess the percentage of infection in clean surgical wounds, one is prone to underestimate the damage, as is well illustrated in Meleney's article.[1] In trying to find the source of the contamination, many problems confront the investigator. Without a doubt, most infections arise from outside of the body, unless some hollow viscus which contains bacteria has been opened. They may be introduced from the air, from contaminated instruments, from the surgeon's hands or from the contiguous parts of the patient's body. To minimize the chances of contamination, all of these sources must be separately and individually studied. To evaluate then the results of such a study, it is necessary to have certain definite standards by which one may judge the character of a wound.

For the purposes of this study a questionnaire was sent to the heads of seventeen teaching surgical services in different parts of the country, setting forth specific questions as to their methods of preparation of

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From the Department of Surgery, Northwestern University Medical School.

1. Meleney, F. L.: Infection in Clean Operative Wounds, Surg., Gynec. & Obst. **60**:269, 1935.

the operative field.[2] They were also invited to submit their definitions of an infected wound.

Gerster,[3] in the introduction to his classic volume "Aseptic and Antiseptic Surgery," wrote: "To a large number of medical men, the aseptic and antiseptic methods present an incongruous chaos of seemingly contradictory and often incomprehensible detail, arbitrary and varying, according to the predilections or whims of this or that teacher." A perusal of the answers to the questionnaires might at first impress the casual reader in a similar manner. But, just as the advent of antiseptic and aseptic surgical methods brought the mortality from amputations from 35 per cent to about 15 per cent, so has the zealous attention to detail in aseptic technic lowered the incidence of serious and of trivial infections of wounds, for instance, in the clinic of Dr. F. Meleney from 4 to 1 per cent for serious infections, and from 10 to 5.4 per cent for trivial infections.[4] Yet Meleney stated: "We do not feel that we have reached the irreducible minimum yet, and will strive to reduce the incidence still farther." There has been no standardization in the preparation of operative fields, and there cannot be as long as surgeons are striving to attain more perfect methods. Nevertheless, some attempt should be made to correlate the procedures and to survey the constructive efforts of teaching institutions.

DuMortier[5] has shown that the resistance of a healing wound to infection is minimal for the first six hours postoperatively. Billroth had already demonstrated that virulent organisms placed on granulation tissue in the dog caused no infection, while the same bacterial strain

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2. Questionnaires were sent to the following men, who represent their respective clinics: Dr. Alton Ochsner, Tulane University, New Orleans; Dr. Charles W. Mayo, Mayo Clinic, Rochester, Minn.; Dr. Elliott C. Cutler, Harvard University, Boston; Dr. Sumner Koch (general surgery), Dr. Loyal Davis (neurosurgery), and Dr. Arthur H. Curtis (gynecology), Northwestern University, Chicago (Passavant Memorial Hospital); Dr. Vilray P. Blair, Washington University, St. Louis; Dr. I. S. Ravdin, University of Pennsylvania, Philadelphia; Dr. Claude S. Beck, Western Reserve University, Cleveland; Dr. Elmer Hess, St. Vincent's Hospital, Erie, Pa.; Dr. Frank Lahey, Lahey Clinic, Boston; Dr. Vernon C. David, Rush Medical College, Chicago; Dr. J. Shelton Horsley, University of Virginia, Richmond, Va.; Dr. Dallas B. Phemister, University of Chicago, Chicago; Dr. Frederick Christopher, Northwestern University, Chicago; Dr. R. W. McNealy, Northwestern University, Chicago; Dr. Owen H. Wangensteen, University of Minnesota, Minneapolis; Dr. Hugh McKenna, Northwestern University, Chicago; Dr. John Hartzell, Detroit.

3. Gerster, A.: The Rules of Aseptic and Antiseptic Surgery, New York, D. Appleton & Co., 1888.

4. Meleney, F. L.: The Control of Wound Infections, Ann. Surg. **98**:151, 1933.

5. DuMortier, J. J.: The Resistance of Healing Wounds to Infection, Surg., Gynec. & Obst. **56**:962, 1933.

caused extensive infection and death in fresh wounds. It may therefore be emphasized that the technic of the operating theater and the immediate postoperative care are of vital importance in reducing the incidence of infection.

The factors at work are the dosage and virulence of the contaminating bacteria and the resistance of the tissues invaded. This might be called the bacteria-tissue balance. Did not the most powerful bactericidal agents lower the immunity of tissues by damaging them, the equation would be a simple one indeed. The problem resolves itself into a method which will reduce to a minimum the dosage and virulence of the bacteria and yet not damage the adjacent tissues. It is unfortunate that one cannot evaluate the success of the various methods by contrasting statistical results. This will be impossible until some definite criteria of an infection of a wound have been described and some specific method for tabulating results devised.

Almost all of the heads of the seventeen clinics who cooperated in detailing their technic differentiated between clean and infected wounds simply by differentiating healing by primary and that by secondary intention. The heads of two services stated that they depended on laboratory examination to determine the presence or absence of bacteria. Another stated that all wounds contain bacteria, so that he could not subscribe to such a differentiation. Definite criteria, valuable for statistical purposes, are employed in only three clinics. In two the criteria are very simple, but in one they are more complex. The criteria of one of the surgeons are: (*a*) the collection of serum or stitch abscesses, (*b*) frank infection not affecting the end-result and (*c*) complications of the wound affecting the end-result.

This surgeon added: "This rule is rigidly adhered to and reported on at the meeting of the junior members of the surgical services, and discussed at the monthly meeting of the surgical staff."

Another of the surgeons classified infected wounds into (*a*) wounds which in no way disturb the ordinary processes of healing, such as stitch infections, and (*b*) deep infections, which require opening of the wound for drainage.

One surgeon reported a complete system which, I believe, is well worthy of general adoption, if it is accurately carried out by the attending and resident staff: All wounds are classed into three groups: (*a*) clean wounds, such as those made for hernia, thyroidectomy, etc.; (*b*) partially or potentially contaminated wounds, such as those made in operations on the bowel, bladder, etc., (*c*) wounds in a grossly infected field, such as those made for abscess, empyema, etc. These are subheaded by the following code: (0) healing by primary intention; (1) secondary hemorrhage; (2) sterile hematoma; (3) hematoma which becomes infected after evacuation; (4) minor infections of the

wound, such as a stitch abscess (5) moderate infection; (6) serious, spreading infections of the wound; (7) disrupted wound; (8) necrosis of the skin, and (9) a persistent sinus or fistula. Thus a hernia which heals without any evidence of infection would be classed as A0; a hernia with a stitch abscess as A4, and a disrupted wound following a perforated gastric ulcer as B7. This surgeon considers a wound infected if it exudes as little as a drop of serum or shows the slightest amount of inflammation around a stitch. He further stated that it is the finding at his clinic that this system focuses the attention and stimulates close observation of wounds by the staff.

Some classification as this is urgently needed if uniformly good results are to be obtained. Simply to differentiate between primary and secondary union is not sufficient. Colp[6] expressed the opinion that infection of the wound does not play a major rôle in disruption of the wound. Grace,[7] however, found infection of the wound to blame in seventeen of forty-six cases of a similar nature. Yet most of the wounds which healed did so by secondary intention, irrespective of infection.

What are the precautions which are used in the general operating room in these seventeen clinics? The sterilization of linens and instruments has been omitted from consideration, for this has become fairly well standardized and is easily amenable to bacteriologic check. The scrubbing technic has also been eliminated, as this too is more or less standardized, although the relative merits of the dry and wet glove technics are still a matter of controversy.

GENERAL OPERATING ROOM TECHNIC

In fifteen of the seventeen clinics the heads of which responded to the questionnaire, the same room is used both for clean and for septic operations. In all these fifteen an attempt is made to perform the clean operations first. When an operating room has been contaminated, an isolation technic is the rule. In most of the institutions the furniture and floor are washed with either the compound solution of cresol U. S. P. or a 5 per cent solution of cresol, the dirty linen is soaked in compound solution of cresol, the clean linen is autoclaved and the soiled gauze is burned. The report from one clinic is in such detail that it is well worth repeating.

> Linen, instruments, gloves and contaminated supplies are placed on the operating table by a nurse in gown and gloves and taken to a special work room, where linen and gauze are placed in a 10 per cent solution of cresol for one hour. Instruments and gloves are washed in cold water and boiled: instruments for fifteen minutes,

6. Colp, R.: Disruption of Abdominal Wounds, Ann. Surg. **99**:14, 1934.
7. Grace, R. V.: Disruption of Abdominal Wounds, Ann. Surg. **99**:28, 1934.

gloves for ten. Scalpels, pins, etc., are placed in a 40 per cent solution of cresol for one hour. The rubber pillow and operating table are washed with a 5 per cent solution of phenol. The floor is mopped with soap and water and 5 per cent phenol. The mop is treated with 5 per cent phenol and then sent to the laundry.

In twelve of the seventeen clinics all of the members of the operating team are required to wear special shoes in the operating room. In the five in which this requirement is not made nearly all of the men do so anyway. In one clinic the members of the attending staff but not of the house staff are required to wear special shoes.

In all of the clinics the visitors in the operating room, are required to wear special gowns, but in only eight are the interns required to don gowns while observing. In all the clinics visitors are required to wear caps, and in all but one they are required to wear masks. Four of the surgeons were very emphatic on this point and suggested its emphasis. In only one institution was there no requirement that the mask must cover the nose. The head of one clinic especially mentioned that each visitor to the clinic is personally and specially informed that the mask should cover the nose.

The heads of only two clinics stated that they had no difficulty in enforcing these regulations. In seven of the clinics the responsibility of enforcement is placed on the supervisor, and the cooperation of the staff is invited. The head of one clinic wrote "upon suggestion, then request of the surgeon." In one clinic notices are posted, and in two the head of the department personally enforces the rules. In one clinic there is a special officer of the day to enforce the operating room regulations.

The size and type of ligature material in the subcutaneous tissues have been accused of being a predisposing factor in many cases of infection of the wound, and therefore, the type used was asked of the different surgeons. Four of the surgeons use 00 plain catgut exclusively, while three use 0 plain catgut. Three surgeons used 000 plain catgut, while two use from 0 to 2 plain. One surgeon uses from 00 to 00000 plain catgut, and one uses either 00 plain or fine silk, while another uses only fine silk material.

OPERATIONS ON THE ABDOMEN, THORAX AND EXTREMITIES

Operations on different parts of the body require special technic of preparation. As the skin of the trunk and that of the extremities are somewhat similar, operations involving these parts are classed together. Only in one clinic is no preparation carried out on the evening previous to the operation. In seven clinics the operative field is cleaned with soap and water and shaved. In four clinics preoperative preparation is carried out only in cases in which clean bone is being dealt with, and in these cases a dressing moistened with 70 per cent alcohol is

applied for twelve hours preoperatively. In two clinics the area is washed with soft soap and water, shaved and cleaned with benzine, ether and alcohol, and then a sterile binder is applied. In one clinic the area is shaved and washed with soap and water, and then a sterile binder is applied.

In only one clinic is the preoperative preparation done in a special preparation room.

I have chosen to divide the solutions used on the skin and mucous membranes into two classes, the lipolytic, or cleansing, agents and the bactericidal agents. By the first are implied those compounds and solutions which remove oils and detritus from the surface of the skin, and with them mechanically remove organisms which reside therein as opportunists. Thus they mechanically reduce the dose of bacteria which the operator may introduce into the deeper tissues. Most of these are not significant in reducing the vitality of the subadjacent tissues and therefore do not affect the bacteria-tissue equation. Most potent bactericidal agents do, to some extent at least, injure normal tissue, thus influencing the equation. Bactericides are therefore considered separately.

The heads of three clinics reported that they do not employ any cleansing or lipolytic agents before the application of a bactericidal agent. In all of the clinics, however, some mechanical cleansing is used on the evening preceding a planned operation. In twelve clinics a cleansing or lipolytic solution is used. In another clinic, soft soap diluted with sterile water (1:6), copiously lavaged with sterile water, and with no other agent, is used. In three other clinics soft soap is used, but in two the surface is sponged with ether and in one with alcohol followed by ether. In four clinics benzine is used followed by ether. In one of these clinics iodine is added to the benzine in the concentration of 1 drachm (3.7 cc.) to a gallon (3,785 cc). In three clinics alcohol is used followed with ether. In one clinic merely 70 per cent alcohol is used.

In seven of the clinics tincture of iodine is employed as a bactericidal agent. In one clinic tincture of iodine is alternated with tincture of metaphen. In all cases the concentration of the tincture of iodine is 3.5 per cent (which is sometimes referred to as "half strength iodine"). In two of the clinics the excess iodine is removed with 70 per cent alcohol, while in one clinic it is removed with Richardson's solution. In two clinics tincture of merthiolate is used exclusively. In two clinics solutions of the mercury bichloride are employed, in one in a concentration of 1:4,000 and in the other in a concentration of 1:1,000. In the latter institution this is followed by three paintings with 70 per cent alcohol and then with 3.5 per cent tincture of iodine in the umbilicus in cases of abdominal operations, or on the nails in cases of operative procedure

on the extremities. In one clinic a 5 per cent solution of trinitrophenol is used, while in another a 1:2,000 solution of mercuric oxycyanide is employed. One surgeon does not use any bactericidal agent, believing that mechanical cleansing and lipolysis are sufficient and that the bactericidal agents damage the tissues sufficiently to throw the bacteria-tissue equation into the favor of the former.

The actual preparation of the field is done by a "scrubbed" assistant or by the surgeon in fifteen of the clinics, while in two it is done by an "unscrubbed" nurse.

In sixteen of the clinics the edges of the wound are protected by skin towels. In only one are towels entirely dispensed with. In four of the institutions the towels are made of linen, in two of Bates muslin, and in two of plain cotton toweling, in one of cotton huck and in another of birdseye cotton. In three clinics laparotomy pads are used, and in another waterproof cellophane is used in operations for gastro-intestinal conditions. According to the technic in six of the clinics the towels are applied immediately after the incision in the skin is made, and in five, after the exposure of the deep fascia. In one clinic they are applied to the adjacent skin just before the incision is made, and in one, just before the peritoneal cavity is opened. One surgeon uses a sterile stockinet on the extremity, which is incised with the skin. In eight clinics the towels are fastened to the edges of the skin by Backhaus towel clamps, while in four institutions they are clipped to the edges of the skin with Michel clips. In one service they are applied to the edges of the deep fascia by clips.

In thirteen institutions the scalpel which has opened the skin is always discarded. It is usually discarded in two clinics and is not discarded in two other clinics. In only one clinic is any bactericidal agent used on the skin before the closure is made, and in this case tincture of merthiolate is used.

As a postoperative dressing, all but three surgeons use dry gauze. Two use silver foil, while one occasionally uses an alcohol dressing.

OPERATIONS ON THE CRANIUM

The heads of five clinics stated that no preparation is carried out on the evening preceding an operation on the cranium. In nine clinics the field is shaved and scrubbed with soft soap and water, and then sterile dressings are applied. In one clinic, after the shave and wash, benzine and ether are applied before the application of a sterile dressing. For the immediate preoperative preparation soap and water are used as a lipolytic agent in only one clinic. In four of the clinics ether is used; and in three this is followed with 70 per cent alcohol, while in one 90 per cent alcohol is employed. Benzine followed by ether is used in one clinic.

In six clinics 3.5 per cent tincture of iodine is used as a bactericide, and in four a part of the iodine is removed with alcohol. Tincture of merthiolate is used in two clinics, while the use of a 3 per cent solution of trinitrophenol, mercuric oxycyanide, and 1:4,000 mercury bichloride is reported from other clinics. In one clinic the new antiseptic solution suggested by Vaichalis and Arnold,[8] which has mercuric iodide as a base, is used.

In all but one service skin towels are used to protect the edges of the wound. In two, towels are used which are soaked in a solution of mercury bichloride. In five, they are sutured to the edges of the skin, while in another five clips are used. In two clinics they are clipped to the galea.

In all of the services the scalpel used for the incision is discarded. In six clinics silver foil is used as the postoperative dressing, while in six others dry gauze is used. In one clinic alcohol dressings are used.

OPERATIONS ON THE FACE

In nine clinics no preparation is carried out on the evening preceding operation on the face. In five clinics the area is carefully shaved, and in one the hair in the nostrils is always carefully clipped. In one clinic the face is shaved and washed with soft soap and water and then with benzine, ether and alcohol, and a sterile dressing is applied, the location of the operative field permitting.

Three surgeons advise the use of soap and water as the lipolytic and cleansing agent, which in one clinic is followed by benzine and in another by a mixture of ether and acetone. In one clinic benzine is used and in another ether followed by alcohol. In others no lipolytic agents are used. In one clinic alcohol (70 per cent) only is used as a bactericide, while in a second clinic alcohol alone is used only on children. In five clinics tincture of iodine is used, in four of them the 3.5 per cent and in one the 2 per cent tincture.

In three services the iodine is removed with alcohol, and in one, with Richardson's solution. In two institutions mercury bichloride is used, while in two the tincture of merthiolate is employed. In one a 1:200 tincture of metaphen is used and in one, mercuric oxycyanide.

Skin towels are used by eight surgeons, three of whom clip them to the edges of the skin, while in one clinic they are simply laid on and held over the edges of the skin. Three surgeons use silver foil as the postoperative dressing, while ten surgeons use dry gauze. One surgeon advocates a collodion seal, while one does not use any dressings at all.

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8. Vaichalis, J. A., and Arnold L.: Compound Solution of Mercuric Chloride for Skin Disinfection, Surg., Gynec. & Obst. **61**:333, 1935.

OPERATIONS ON THE ANUS

In six clinics preparations for anal and perineal surgical procedures on the evening preceding the operation consist of shaving and scrubbing the perianal skin with soap and water. The rectal canal is prepared in some way in all of the institutions. In one, irrigations with tap water are started thirty-six hours before the operation. In nine of the clinics, however, enemas of saline solution are given on the evening preceding the operation, until they return clear. Then a single enema is given on the morning of the operation. In contrast to this, in one clinic the use of only one cleansing enema is advised. One surgeon starts with a soap-suds enema, which is followed by lavages with saline solution until they return clear, and then a 2 per cent aqueous solution of mercurochrome is instilled. One report stated that on the evening preceding operation 2 ounces (30 cc.) of sweet oil is instilled into the rectum through a catheter, followed by a pint of water (473 cc.). A similar enema is given two hours preoperatively.

It seems interesting and perhaps even significant that in six clinics a routine preparation of the vagina in the female precedes rectal operations. Even if only the anus is to be the site of the operative field, one must consider that the field may become contaminated by infective leukorrheal secretions which pour from the vagina. In two cases this preparation consists in scrubbing with soft soap followed by a douche of sterile water. In one clinic the use of soap is followed by application of 50 per cent alcohol and in another by a douche with a compound solution of cresol. In two clinics the vagina is painted with a 3.5 per cent tincture of iodine under direct vision with a speculum.

Soap and water are used as a lipolytic agent on the perianal skin in seven clinics. In two clinics ether and benzine are advocated. In one clinic no further bactericidal agent is used, while in four 70 per cent alcohol is employed. In five clinics 3.5 per cent tincture of iodine is used, the iodine being removed with 70 per cent alcohol in one. Tincture of merthiolate is used in two clinics, and mercury bichloride in two others; in one alcohol is used first in cases in which general anesthesia is given, while in cases in which local anesthesia is employed soft soap is used as the lipolytic agent. Mercuric oxycyanide is used in one clinic, while in another tincture of merthiolate is used around the anus, while the rest of the field is painted with 3.5 per cent tincture of iodine.

In most of the clinics dry drapings are used, but in one institution a moist towel is placed over the genitalia. The postoperative dressing is a simple dry one in all but two clinics. In these, warm boric acid dressings are used. In ten clinics no constipating agent is used postoperatively. In one liquid petrolatum is given by mouth immediately, and an olive oil enema is given daily for one week.

OPERATIONS ON THE SCROTUM AND PENIS

In seven clinics no preparation of the field is carried out on the evening preceding surgical intervention on the scrotum and penis. In six clinics the patient is shaved and given a bath. In only three clinics are sterile dressings applied. In six clinics soft soap and water are used as the lipolytic agent. In two clinics benzine and ether are used, and in one, a solution of benzine and iodine containing 1 drachm of iodine to a gallon of benzine.

As the bactericidal agent, only one surgeon occasionally uses a "very weak" solution of iodine. Three advocate the use of a 1 : 4,000 solution of mercury bichloride, following this with 70 per cent alcohol, while one uses a 1 : 2,000 solution of mercuric oxycyanide. In three clinics the alcohol-acetone solution of mercurochrome in a strength of 5 per cent is used. In two clinics simply 70 per cent alcohol is used, while in one, merely acetone is employed. In one clinic no bactericidal agent is used. Skin towels are applied in eleven clinics.

OPERATIONS ON THE VAGINAL CANAL

In only three clinics is no preparation of the field done on the evening preceding operation on the vaginal canal. In most of the clinics the patient is shaved, and then some kind of douche is given. Boric acid proves to be the most popular, although sterile water and a dilution of compound solution of cresol U. S. P. (0.5 per cent) are close seconds. In one clinic a douche of a compound methol powder is used.

In twelve clinics the rectum is prepared by the use of enemas, until they return clear. In four clinics no preparation of the rectum is attempted.

The preparation of the field with lipolytic and bacteriostatic agents presents several problems. In the first place there are two types of tissue to be prepared, a sensitive mucous membrane and a resistant skin. The vaginal canal may be prepared by simply pouring the lipolytic and cleansing agents into the tract, or it may be painted carefully under full vision by the use of a speculum. If the former method is used, one must consider the possibility of washing living bacteria and débris into the vagina as the solution runs over the mons veneris and the labia. Therefore, this problem was an extremely interesting one to investigate.

In six institutions soft soap and water are used, the suds being poured into the vagina, and then the adjacent skin as well as the vaginal tract is scrubbed. Other clinics do not use any lipolytic agent. Douches are used in two clinics, consisting of either a dilution of compound solution of cresol U. S. P. (2 per cent) or a saturated solution of sodium borate. In both cases these are poured into the vagina with a standard rubber douche tip and the vagina is painted with tincture of

iodine under vision by the use of a speculum. The surrounding skin is then prepared with the tincture of iodine. In seven other clinics careful painting of the vaginal tract with tincture of iodine in a 3.5 per cent concentration is advocated, a 70 per cent alcohol being used for its removal in six clinics, and Richardson's solution in one. The surrounding skin is then prepared in a similar manner. In two of these clinics the iodine is alternated with mercurochrome in the alcohol-acetone solution, or with a 1 : 1,000 tincture of merthiolate. In one clinic mercury bichloride is applied blindly through swabs soaked in the solution. In another a similar technic is used but is followed with accurate painting of the vaginal tract with Churchill's iodine solution (containing 15 per cent iodine) under direct vision by use of the speculum. In one clinic mercuric oxycyanide is painted on the vaginal wall through a speculum. In another 70 per cent alcohol is poured blindly into the vagina and carried into all parts of the canal by swabs; the surrounding skin is then painted with tincture of merthiolate. In only one clinic is there no provision to keep the solutions from pouring over the mons veneris or labia.

In the postoperative care a "wet technic" is used in only three institutions. None of the reports indicate any special method of exclusion of the anus from the operative field except by draping.

COMMENT

From a review of the answers to the questionnaires, one can glean many significant points. Perhaps the most valuable one is the evident interest and care which most of the large teaching institutions display in their attempt to minimize the chances of contamination of the wound from sources outside of the body of the patient. This certainly should be emulated by smaller hospitals, especially those of the "open staff" type, as these are handicapped in having the responsibility for surgical complications divided among individual surgeons.

Lister was of the opinion that much of the contamination of the wound came from the air in the operating room and therefore used sprays of bactericidal solutions. Meleney stated, however, that contamination from the air was found to be a minor factor in comparison with other sources in the early days of aseptic surgery. When the other sources of bacterial contamination had been eradicated or minimized, contamination from the air again assumed a major rôle. Meleney [8] and Davis [9] have conclusively shown that serious infection of the wound may have its origin in the mouths and noses of the personnel of the operating room and of visitors. Meleney found that

9. Davis, J. S.: The Importance of Adequate Masking During Operations, Ann. Surg. **100**:1008, 1934.

when, because of the obvious discomfort, he had permitted the anesthetists to remain unmasked, the incidence of infection of the wound definitely rose. Now he permits no exceptions to the rule of wearing a mask over the nose and the mouth. Walker [10] has examined masks submitted from sixty hospitals in the United States and found that "none could be considered as efficient in preventing the passage of organisms through the material." But a mask containing an impermeable membrane such as described by Blatt [11] is difficult to use because of the discomfort, and the 6 ply fine mesh mask will prohibit droplet infection. But the all-important factor is that masks should be worn by all persons in the operating room and worn so that both the nose and the mouth are covered. Talking and lecturing will necessarily increase the possibility of droplet infection, but in all probability the contamination from the air is enhanced most by the shuffling about of people in the operating room, opening and closing of doors, etc.

The wearing of a different pair of shoes in the operating room seems to be a factor to be considered, as emphasis seems to be placed on this point in twelve of the clinics. Unquestionably street dirt will be carried into the operating room from street shoes and new bacterial flora added to that already present in the dust of the operating room. It is perhaps even more significant that shoes and other articles of apparel which have become contaminated in doing unclean dressings must at least be covered when a person enters the operating room. The interns may come into the operating room wearing the same uniform in which they have just dressed a purulent wound or assisted at an autopsy, stand directly behind the surgeon or assistant and even touch his gown, and thus transmit bacteria into a sterile field.

The amount, type and size of the foreign material in the form of ligatures are definitely a factor in the prevention of infection. The controversy between the relative merits of silk and catgut still rages. Whipple [12] and many others [13] have been emphatic in their championship of fine silk as ligature and suture material. Yet it is notable that only two of the clinics here surveyed have adopted silk.

The preparation of the field itself resolves itself into several factors of varying importance. In planned, nonimperative operations, the removal of superficial detritus and shaving of the area are believed by the majority of the surgeons to be best carried out on the evening preceding the operation. This permits the sealing over of small abra-

10. Walker, J. J., in discussion on Meleney.[1]

11. Blatt, M. L.: A New Face Mask, Surg., Gynec. & Obst. **57**:234, 1933.

12. Whipple, A. O.: Use of Silk in the Repair of Clean Wounds, Ann. Surg. **98**:662, 1933.

13. Halsted, W. S.: Ligature and Suture Material: Employment of Fine Silk in Preference to Catgut, J. A. M. A. **60**:1119 (April 12) 1913.

sions which may have been produced by the preliminary scrubbing, which, it has been repeatedly emphasized, should be as gentle as it is thorough. In almost every clinic the use of some lipolytic agent, which acts as a mechanical cleanser as well, is deemed advisable in the first preparation of the field. In one clinic this is believed to be sufficient preparation. The surgeon at the head of this clinic is of the opinion that all the bactericidal agents do definite damage to the vitality of the tissues. It has been repeatedly demonstrated that there is no bactericidal agent which will completely sterilize the skin. Thus, he feels that the bacteria which remain will find excellent culture mediums in the devitalized tissues.

The variety of the bactericidal agents used by the surgeons who answered the questionnaires is rather large. Their sequence and concentration vary somewhat. This may be considered as an indication that a thoroughly satisfactory agent has not yet been found. Until there is some in vivo standardization of results, their relative merits defy scientific evaluation.

It has been practically demonstrated that the tissues surrounding a wound cannot be completely sterilized by any methods now in use. Bacteria still remain deep in the sweat glands. Without doubt, in almost every operative procedure performed under the influence of a hot source of illumination and an anesthetic the patients perspire freely. The bacteria-laden sweat is readily swept into the wounds by the hands of the surgeon or by instruments, sponges, etc. It therefore seems significant that almost in every case mention was made that the wound is isolated from the surrounding cutaneous surface by skin towels.

SUMMARY

The aseptic technic is not a simple routine accomplished by wearing gloves and pouring an antiseptic solution on the operative field. It is rather a complex of carefully planned and meticulously carried out procedures. Only by vigilant attention and progressive thought to detail can the incidence of wound complications be diminished to a hypothetic "irreducible minimum."

The actual evaluation of the different procedures which have been discussed is difficult or impossible until some classification of such complications has been adopted, and careful studies of wound morbidity with various technics are reported. This demands the serious attention of all surgeons to the process of wound healing.

It seems unfortunate that all attendants as well as the surgical team do not sedulously regard the possibility of seriously increasing the morbidity as well as the mortality of surgical procedures by adhering to even the more simple principles of operating routine. The most

commonly observed violation and perhaps the most dangerous is the omission of the nose mask. Until such rules are automatically followed, rigid supervision is an absolute necessity. Some persons in the operating room should in every case be given the responsibility of securing the full cooperation of the attending and the resident staff as well as of the visitors for the attainment of the most perfect technic possible.

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LESIONS OF THE THYROGLOSSAL TRACT

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The relative infrequency and the perplexities of diagnosis combine to make lesions of the thyroglossal tract an unusually interesting group of pathologic changes. In many instances it is impossible to make an accurate and complete differential diagnosis preoperatively, owing to the close similarity of the lesion to a tumefaction arising in the midline of the neck anteriorly and to the lack of specific evidence to set any one of the lesions apart. Greater familiarity with the characteristics of lesions of the thyroglossal tract should aid in their recognition and treatment.

Adequate reason for the existence of a lesion of the thyroglossal tract is found in a study of the embryology of the thyroid gland. Meyer,[1] by his able summary of this subject, and Wenglowski,[2] through his masterful study of the development of the thyroid, have greatly clarified a controversial problem. Briefly, it appears from the former confusion that the anlage of the thyroid arises between the open ends of the second and the third branchial arch that form the base of the tongue. In the embryo of 2.6 mm. the anlage may be seen growing downward from this so-called furcula. Whether or not the structure is tubular [3] or solid [4] is of little consequence to this study. In the embryo of 6.5 mm. studied by Wenglowski the anlage is completely separated from the floor of the mouth and shows beginning division into right and left parts. The strand connecting the anlage with the pharyngeal floor normally segments and disappears at this stage, but if some cells fail to vanish they may give rise to the lesions here discussed. When this downward growth takes place there is a mechanical dragging in of the epithelial elements of the pharynx, i. e., squamous or ciliated cells with their associated characteristics of lymphoid tissue and mucous glands.

The development of the hyoid bone beginning in the fifth week of embryonic life is of great importance. The cells of this bone develop

1. Meyer, H. Willy: Congenital Cysts and Fistulae of the Neck, Ann. Surg. **95**:1-26 (Jan.); 226-248 (Feb.) 1932.

2. Wenglowski, quoted from Meyer.[1]

3. Baumgartner, C. J.: Branchial and Thyroglossal Duct Cysts and Fistula in Children, Surg., Gynec. & Obst. **56**:948-955 (May) 1931.

4. Norris, E. H.: The Early Morphogenesis of the Human Thyroid Gland, Am. J. Anat. **24**:443-465, 1918.

dorsal to the already existing thyroid strand, and the two become intimately related. Further growth of the hyoid bone and its rotation to assume its adult position cause the strand, now fused with the periosteum of the anterior surface, to be compressed and drawn posteriorly. The continuity of the thyroid strand is thus definitely broken. This fact is of significance when treatment is considered and also because a division point is formed below which about 75 per cent of the lesions occur.[5]

It is natural when dealing with a lesion of faulty development that other etiologic characteristics are of little differential importance. Thus, the two sexes are about equally affected, in spite of a few reports that mislead the reader to believe that males predominate.[6] Likewise, a lesion of the thyroglossal tract usually appears during the earlier years of life, although the developmental abnormality may remain quiescent for a long period before being stimulated to grow. For this reason lesions are reported as appearing from the first to as late as the eighth decade.[7]

Reference has been made to the comparative rarity of abnormalities of the thyroglossal tract. Sistrunk[8] recorded thirty-one cases observed in eighty-six thousand consecutive patients seen in the Mayo Clinic. Clute and Cattell[7] reported seventy-four cases seen among sixty-five hundred patients with goiter. The small group here recorded were observed while twenty-five hundred patients with goiter were being treated. Studies carried on at the present time indicate that the lesions could appear with much greater frequency, but the stimulus to grow is fortunately lacking in the vast majority of persons.

Because the thyroid gland begins in the base of the tongue and finally rests near the base of the neck, it is obvious that cell remnants anywhere along this course may produce lesions in later years. As noted, most of the changes appear below the hyoid bone, where commonly the tumefaction is cystic. Either spontaneously or, far more commonly, as a result of a surgical procedure, a sinus may develop from this cystic swelling. Fistulas have been reported.[8] Heterotopic thyroid tissue may

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5. Bailey, H.: Case of True Congenital Thyroglossal Fistula and of Subhyoid Thyroglossal Cyst, Proc. Roy. Soc. Med. **18**:6-7 (Oct.) 1924.

6. (*a*) Rankin, F. W., and Crisp, N. W.: Diagnosis and Surgical Treatment of Cysts of the Thyroglossal Duct, West. J. Surg. **40**:105-109 (March) 1932. (*b*) Klingenstein, P., and Colp, R.: Congenital Cysts and Fistulae of the Neck, Ann. Surg. **82**:854-864, 1925.

7. Clute, H. M., and Cattell, R. B.: Thyroglossal Cysts and Sinuses, Ann. Surg. **92**:57-66, 1930.

8. Sistrunk, W. E.: The Surgical Treatment of Cysts of the Thyroglossal Tract, Ann. Surg. **71**:121-123, 1920.

be found along the path of the embryonal strand, and reports of lingual thyroid tissue are not uncommon.[9]

The gross pathologic appearance of the lining wall of the cyst is smooth and shiny; thyroid tissue may be found within the wall. The contents are usually so modified by secondary infection that the original pathologic process is greatly obscured. Usually the cystic content is necrotic material, in which cholesterol crystals may be present. Histologically, the cyst is lined by squamous epithelium or infrequently by ciliated cells. Secondary infections occur so often that chronic inflammatory changes are usually present within the wall of the cyst.

A swelling in the neck is the only complaint of a patient with such a cyst unless infection is present. Secondary infection usually follows incomplete operative removal, with the formation of an intermittently or persistently draining sinus tract. In a few cases incision and drainage of a spontaneously occurring abscess will be necessary before removal can be attempted. This was true of nine cases in a series of two hundred recorded by Rankin and Crisp [6a] and in one of this series.

An accurate clinical differentiation of the tumefactions that appear in the midline of the neck anteriorly is difficult and frequently impossible. The clinical diagnosis is of less importance than recognition of the pathologic process at the time of operation. Surgical treatment is indicated for all patients, but the operative technic varies greatly with the lesion found. A cyst of the thyroglossal tract found low in the neck may simulate a cystic adenoma of the median lobe of the thyroid, and aberrant thyroid tissue in the same location has often been considered as an adenoma of the thyroid. The latter error could easily have been made in the following case:

Mr. K., aged 47, was admitted to the Albany Hospital on Aug. 22, 1935, because of a painless swelling in the midline of the neck. This had been present two months and had not changed noticeably in size. On examination an almond-sized firm enlargement was found to overlie the thyroid cartilage in the midline of the neck. Below this nodule was a pea-sized swelling of the same firm character at the level of the isthmus of the thyroid. A clinical diagnosis of tumor of the thyroglossal tract was made and excision revealed an adenoma, which was proved histologically to be a colloid adenoma, in some areas of which moderate hyperplasia was observed.

It is almost impossible to distinguish a dermoid or a sebaceous cyst, when found in the appropriate place, from a cyst of the thyroglossal tract. Textbooks speak of attachment to the skin by sebaceous cysts and of adherence to the deep fascia by dermoid cysts, but it may be most difficult to demonstrate these qualities in a given case. Movements of

9. Cattell, R. B., and Hoover, W. B.: Lingual Thyroid Gland, S. Clin. North America **9**:1355-1362, 1929. Lahey, F. H.: Lingual Goiter, Surg., Gynec. & Obst. **36**:395-397 (March) 1923.

the cyst during deglutition may likewise be of little aid. In both the following cases a clinical diagnosis of cyst of the thyroglossal tract was made in spite of careful attention to these supposedly differentiating points.

Mr. W., aged 23, was admitted to the Albany Hospital on May 7, 1935, because of a swelling in the neck of eight years' duration. There had been no symptoms except a slow increase in size. On palpation an egg-sized systic swelling in the midline of the neck anteriorly was present just below the hyoid bone. The cystic mass was excised, and pathologic examination confirmed the operative diagnosis of dermoid cyst.

B., aged 5 years, was brought to the Albany Hospital on June 28, 1935, by her mother, who had discovered a small nodule in the midline of the neck. This had been present two months without symptoms or change in size. A deep-seated soft nodule, too small (1 cm. in diameter) to elicit fluctuation, could be seen and felt at the level of the superior border of the thyroid cartilage in the midline of the neck anteriorly. Again pathologic examination confirmed the operative diagnosis of sebaceous cyst.

The differential diagnosis, then, of a lesion of the thyroglossal tract is hazardous, and mistakes will be made in spite of great care. Clinical errors, such as have just been recorded, are unavoidable, but they can be corrected at operation without endangering the ultimate cure of the patient.

TREATMENT

The ability to interpret accurately the gross pathologic process will determine not only the success of the cure but the technic employed to bring about the cure. For a lesion of the thyroglossal tract Sistrunk [10] advised radical removal with resection of the midportion of the hyoid bone and excision of a core of tissue through the tongue. Beer [11] suggested nearly the same procedure in the same issue of the *Annals of Surgery* that carried the original article by Sistrunk. For a lesion which does not originate in the thyroglossal tract, such as a dermoid or a sebaceous cyst, simple excision will result in complete relief.

The radical method of Sistrunk, in spite of the good functional result, as indicated by Bailey,[12] may well be reserved for those cases in which a pathologic process above the hyoid bone is grossly demonstrable. From the experience in the cases here reported, a simpler procedure is less distressing to the patient, is easier of accomplishment by the surgeon and effects a cure in those cases in which the only changes observed are below the hyoid bone. The technic in such cases is total excision

10. Sistrunk, W. E.: Technique of Removal of Cysts and Sinuses of the Thyroglossal Duct, Surg., Gynec. & Obst. **46**:109-112, 1928.

11. Beer, E.: Excision of the Thyroglossal Duct Sinus, Ann. Surg. **71**:218-221, 1920.

12. Bailey, H.: Complete Eradication of the Thyroglossal Tract, Brit. M. J. **2**:138-139 (July 25) 1931.

of the cyst together with all tissue which has its origin in the thyroglossal tract and extends up to the hyoid bone, where the base of the tract or duct is cauterized. This method was followed in the cases in this series, and as yet no recurrences have appeared.

REVIEW OF NINE CASES

Nine cases, of which four were in males and five in females, are summarized. The age of the patients varied from 8 to 50 at the time of treatment, but the age at the onset of the lesion varied from birth to 49. Three cases appeared in the first decade of life, two in the second, one in the fourth and three in the fifth. The duration of symptoms varied from two months to thirty years, the average being nine and one-half years. Two patients had been subjected to a previous incision, excision had been attempted on one twenty-seven years before admission, and all three had experienced intermittently draining sinus tracts. The lesion in one case was associated with a branchial cleft sinus and in another case with a pilonidal sinus. Two patients discovered the swelling after an acute infection of the upper respiratory tract. The only complaints, except when infection had occurred, was swelling.

On examination these lesions were found from the suprasternal notch to the level of the hyoid bone. Two were in the suprasternal notch, five over the thyroid cartilage and two immediately below the hyoid bone. They varied in size from a narrow sinus tract to that of a lemon-sized cystic mass.

Excision of the cyst together with the sinus tract, when present, was done in each case, the method indicated previously being used. In each instance the pathologist reported a cyst or sinus of the thyroglossal tract. In six cases there was an acute or a chronic inflammatory reaction in the tissue of the wall of the cyst.

SUMMARY

1. Tumefaction arising in the midline of the neck anteriorly requires surgical treatment. Differential diagnosis clinically will often be impossible, but accurate recognition of the lesion at the time of operation is imperative if a cure is to follow.

2. Simple excision of all tissue of the thyroglossal tract below the hyoid bone is sufficient for cure when there is no evidence of a pathologic process above the bone.

The case reports in this paper are presented with the permission of Dr. George E. Beilby, from his private practice in the Albany Hospital.

SIXTY-FIRST REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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This report of progress is compiled from a review of 171 papers selected from 263 titles relating to orthopedic surgery and appearing in medical literature approximately between March 1, 1936, and July 1, 1936. Only those which seemed to represent progress were chosen for review.

CONGENITAL DEFORMITIES

Treatment of Congenital Elevation of the Scapula.—Seaphetti[1] reports 4 cases of congenital elevation of the scapula in patients aged 4½, 6, 13 and 13 years, respectively. An operation for the correction of this deformity was performed by Putti, whose technic is as follows: A curved incision is made from above the superior angle of the scapula downward convexly toward the spine to below the inferior angle of the scapula. After the fascia and the subcutaneous tissues are divided, the mesial and inferior portions of the trapezius muscle are cut from the scapula and, with the superior portion of the latissimus dorsi muscle, are retracted mesially. The rhomboid muscles are then cut from the scapular attachments. The bridge of bone extending from the superior angle of the scapula to the lamina or the transverse process of the third dorsal vertebra is resected. The scapula is drawn downward to its normal position and maintained by two silk or heavy catgut sutures, one of which is passed through the inferior angle of the scapula and sub-

1. Seaphetti, O.: Chir. d. org. di movimento **21**:287, 1935.

periosteally around the fifth or sixth rib and the other from the superior angle of the scapula to the fascia of the erector spinae muscle. In closing the wound, the rhomboid muscles are resutured to the scapula. If necessary, a plastic myotomy is done on the trapezius muscle to obviate an upward pull. A plaster shoulder spica is applied. Roentgenograms and photographs accompany the article by Seaphetti. The operation is done for cosmetic and functional purposes. It is the opinion of Putti and of Seaphetti that in cases of congenital elevation of the scapula, as in those of all congenital deformities, the operation should be done as early as the lesion is recognized to prevent secondary deformities, such as scoliosis. The results, as judged from the roentgenograms and photographs, appear to be excellent.

[ED. NOTE.—The operative procedure presupposes the existence of a bony bridge from the scapula to the vertebra; this exists in a few of the cases in our experience. It is not always possible to correct the deformity with the more extensive periscapular liberating method of Schrock. It is doubtful whether this simpler and less complete procedure would suffice in all cases.]

Radio-Ulnar Synostosis.—Sorokin [2] recognizes two types of radio-ulnar synostosis. They can best be differentiated roentgenographically. In the first type the radius has no formed head, the upper end of the radius being fused wholly with the coronoid process of the ulna for from 2 to 6 cm. This type of deformity is shown best in lateral roentgenograms. In the second type the head of the radius is deformed, the radius being fused to the ulna only in the region of the tuberosity. Other exostoses are often present along the radius. Radio-ulnar synostosis is a congenital deformity frequently associated with other osseous abnormalities. Three cases are reported in detail, and a review of the literature is given.

Tarsal Ossification in Patients with Congenital Clubfoot.—Müller [3] followed the development of the feet in 57 patients with clubfoot for five years. The ossification of the tarsal bones was followed serially in 6. In 5 there was a retardation of ossification of the third cuneiform bone. In 1 there was a general delay of ossification of the distal tarsal bones. Extreme hypoplasia was not found. The first cuneiform bone was enlarged in 10 patients, the enlargement being in direct proportion to the deformity. This seemed to be a compensatory hyperplasia for the injury to the scaphoid bone. In patients treated early, with early resumption of function resulting, no abnormality in ossification was found. There was no evidence of an abnormal anlage in the develop-

2. Sorokin, F. F.: Acta radiol. **17**:191, 1936.

3. Müller, E. W.: Ztschr. f. orthop. Chir. **64**:244, 1936.

ment of the tarsal bones. All changes in the bones were secondary to contractures or to neurologic disturbances.

Extrophy of the Bladder in Relation to Locomotor Function.—Kron [4] studied the pelves of children with extrophy of the bladder to determine what disturbances occurred in standing and walking. With the wide separation of the two rami of the pubis which occurs in this condition, there are a compensatory enlargement of the sacro-iliac joints and marked thickening of both pubic and sacro-iliac ligaments. No functional disturbances were observed, except in the rare instances of pregnancy, with its concomitant relaxation of the pelvic joints.

Genetics of Congenital Deformities.—Lange [5] in a monograph reviews the theories as to the etiology of a great number of congenital malformations. Many data of family trees and the varying geographic distribution of certain congenital deformities are presented. The author gives evidence which suggests strongly that congenital dislocation of the hip and club feet in most instances are inherited. The same is true of many other deformities. The author reasons that the tendency to such deformities is carried as a recessive trait in the physically sound members of families in which such deformities appear. He advocates marriage only with persons in whose family there is no such tendency to deformity in order to prevent this trait from becoming dominant and producing these congenital malformations.

METABOLIC DISTURBANCES OF BONE

Six Years' Experience with Viosterol in the Prevention and Treatment of Rickets, Tetany and Allied Diseases.—A study of several hundred cases of rickets by Shelling and Hooper [6] over a period of six years led to the following findings: 1. For full term infants a daily dose of 5 drops of viosterol was found efficacious in preventing rickets. 2. In a few prematurely born infants and babies growing at a too rapid rate a varied degree of rickets appeared when only from 5 to 10 drops of viosterol was administered daily. The authors, therefore, feel that from 15 to 20 drops of viosterol daily is needed for the first three or four months of life, after which time the dose may be reduced to that given to full term infants. 3. In 134 cases of active rickets in which healing was studied by roentgenograms, the efficacy of a dose of viosterol was found to vary according to the severity of the disease; for example, healing occurred in cases of mild involvement in from one and one-half to two months when small doses were used,

4. Kron, E.: Ztschr. f. orthop. Chir. **64**:201, 1936.

5. Lange, M.: Ztschr. f. orthop. Chir. **63**:1, 1935.

6. Shelling, D. H., and Hooper, K. B.: Bull. Johns Hopkins Hosp. **58**:137, 1936.

whereas in cases of severe involvement from three to five months was necessary, with comparatively larger doses of viosterol. In the group of infants receiving 10 drops daily the healing time was five months; in infants receiving 15 drops, it was four and three-tenths months, and in those receiving 20 drops it was three and one-tenth months; but in the groups receiving from 30 to 60 drops the time was no shorter, indicating that larger doses than 20 drops of viosterol daily were not efficacious in producing more rapid healing. It is interesting to note that when larger doses of viosterol were given in cases of severe rickets deformities of the chest and extremities did not appear. 4. Total refractoriness was not encountered in the entire group, and partial refractoriness was seen in only 1 case. 5. No toxic manifestations were encountered, even though some infants received from 30 to 60 drops daily for several months.

HEMATOGENOUS CHANGES AFFECTING BONE

Changes in the Bone in Sickle Cell Anemia.—Changes in the bone found on roentgen examination in cases of sickle cell anemia and erythroblastic anemia are similar and are not alone diagnostic of either condition.[7] Sickle cell anemia is usually seen in Negro children, while erythroblastic anemia is usually encountered in children of Mediterranean peoples. The prominent changes in the bone consist of changes in the skull, such as thickening of the frontal and occipital areas, and changes in the long bones characterized by cortical thinning, expansion of the shafts and marked medullary trabeculation. Striations were also noted in the pelvis and scapulae. In cases of sickle cell anemia the changes in the bone were found predominantly in the skull.

Changes in the Bone in Leukemia in Children.—The bones of 43 children with leukemia were studied roentgenographically.[8] In 70 per cent of the patients there was a narrow zone of diminished density proximal to the metaphyses of the long bones. There was generalized osteoporosis in 2 patients and slight periosteal elevation in 2 others.

[ED. NOTE.—The aforementioned two articles should be of general interest, primarily as changes in the bone are shown to occur in a rather typical way with numerous generalized diseases.]

TUBERCULOSIS

Tuberculous Cysts of the Knee Joint.—Two cases are reported by Elliott[9] in adults in which roentgenographic examination showed multiple epiphysial cysts of the femur and tibia and the body of the patella.

7. Grinnan, A. G.: Am. J. Roentgenol. **34**:397, 1935.
8. Baty, J. M., and Vogt, E. C.: Am. J. Roentgenol. **34**:310, 1935.
9. Elliott, A. E.: Am. J. Roentgenol. **34**:209, 1935.

These cysts had the appearance of osteitis fibrosa cystica. No other joints were involved. There was no history of tuberculosis elsewhere in the body and likewise no evidence of articular surface damage or disease of the knee joint. In both instances, following a lesser trauma, one of the cysts ruptured into the knee joint. On biopsy, tuberculous infection was proved. In both knees, however, there was preoperative evidence of soft tissue reaction. In one case, after a period of rest, the knee functioned normally for three and one-half years; then after injury generalized tuberculosis of the joints developed.

[ED. NOTE.—This article points out, again, that tuberculous infection of bones and joints may be most atypical and simulate roentgenographically other pathologic processes.]

Tuberculosis of the Acetabulum.—Logroscino [10] reports 3 cases of tuberculous involvement of the acetabulum. Autopsy was performed in 1 of these cases. Excellent roentgenograms and a colored diagram are shown. In cases of this type the lesion starts as a relatively silent and symptomless focus. The lesion may be quite extensive before the hip joint becomes involved. In the case in which necropsy was performed the destructive lesion of the acetabulum was followed by miliary involvement of the cartilage of the acetabulum and the synovial membrane of the hip joint. The lesion may be confined to the area of the acetabulum for a relatively long time, however, before spreading to the joint. In the roentgenograms soft tissue shadows indicated involvement of the joint prior to the changes in the femur, though the lesion in the acetabulum could be seen. The roentgenograms showed areas of increased density in the roof of the acetabulum as earlier lesions followed by progressive areas of lessened density in the central area of the acetabulum. The latter areas were the site of the greatest destruction and the probable site of extension into the hip joint. In this article the literature on the subject is well discussed. While the lesions are considered from every angle, no new ideas as to therapy are suggested. Treatment consisted of plaster spicas.

Tuberculosis of the Rib Cartilage.—From late fetal life onward blood vessels and particularly end-arteries are found to form not only a peripheral but a central network in the rib cartilages. Emboli, as Muhlfelder [11] has shown, may form here. Furthermore, commencing in the third decade marrow begins to appear in the rib cartilages. It may be that in some way this plays a part in localization of the tuberculous lesion in the cartilage. The lesion extends with few symptoms, forms an abscess and discharges and burrows into the intercostal and adjacent tissues, without involving the pleura. Usually no other evidence

10. Logroscino, D.: Chir. d. org. di movimento **21**:527, 1936.
11. Muhlfelder, W.: Deutsche Ztschr. f. Chir. **246**:129, 1936.

of systemic tuberculosis is found. The author adds the reports of 6 cases to the 18 he has collected from the literature. Therapy is surgical. Radical excision is indicated whenever possible. If infection is mixed, preliminary drainage is indicated. Methylene blue outlines sinuses preliminary to extirpation.

Treatment of Tuberculosis of the Bones of the Feet.—Miltner and Fang [12] advocate either amputation or excision of bone in the treatment of advanced tuberculosis of the bones of the foot. The article is based on a study of 147 cases in Chinese, in 86.3 per cent of whom there were draining sinuses on admission. The diagnosis was confirmed by biopsy in 84.3 per cent. In order of frequency, the following bones were involved: os calcis, astragalus, first metatarsal bone, scaphoid and first and second cuneiform bones.

OSTEOMYELITIS

Sclerosing Osteomyelitis Following Fractures.—Swett [13] presents the case histories of 3 patients who had fractures which apparently healed with excessive callus but caused the patient considerable pain on use. Clinically there were local tenderness and local edema. Roentgenograms revealed sclerosis of the bone throughout the original fracture site and across the medulla. Attempts to correct the alinement by open reduction were unsuccessful in relieving pain. Finally, removal of a window of cortical bone which reestablished the medullary canal between the upper and the lower fragment led to recovery. The microscopic study of the removed piece of bone showed focal necrosis. The condition is strikingly similar to sclerosing osteomyelitis described by Garré. This is apparently the first report in the literature of the syndrome occurring in association with simple fractures.

[ED. NOTE.—This finding is very interesting. One questions the use of the term osteomyelitis without more conclusive pathologic data.]

POLIOMYELITIS

Seventh Nerve as a Pathway for the Transmission of Poliomyelitic Virus.—Toomey [14] presents clinical and experimental evidence that the seventh cranial nerve is a possible pathway for the virus of poliomyelitis. Seven patients with poliomyelitis had involvement of the nervous system, which suggested a spread of the virus through the chorda tympani nerve to the nucleus salivatorius, with subsequent involvement of the surrounding neurologic structures. The author was able to produce

12. Miltner, L. J., and Fang, H. C.: J. Bone & Joint Surg. **18**:287, 1936.

13. Swett, P. P.: New England J. Med. **214**:1, 1936.

14. Toomey, J. A.: Seventh Nerve as a Possible Pathway for the Transmission of the Virus of Poliomyelitis, Am. J. Dis. Child. **51**:58 (Jan.) 1936.

experimental poliomyelitis in 5 of 7 monkeys by injection of the virus along the course of the seventh nerve.

CHRONIC ARTHRITIS

Spondylitis Ankylopoietica.—From an examination of roentgenograms, histories and clinical findings of 91 patients suffering from spondylitis ankylopoietica, Golding [15] concluded that the condition might be recognized in the prodromal stage before the spine was affected. Almost all the patients gave a history of pains in the muscles and joints of long duration before the spinal rigidity manifested itself, and in all pathologic changes were present in the sacro-iliac joints. Thirty-three of the patients had pathologic changes in the sacro-iliac joints without involvement of the spine. He concluded not only that the changes in the sacro-iliac joints precede the changes in the spinal cord by a number of years but that some indication of the severity of the disease can be obtained by noting the degree of activity of the process in the sacro-iliac joints.

Roentgen Aspects of Chronic Arthritis.—Spackman [16] describes the roentgenographic appearance of the normal joint and the characteristic changes which occur in rheumatoid arthritis and osteo-arthritis. The findings have been correlated from 1,000 cases. The disease processes are roughly grouped from the roentgenographic standpoint into early, intermediate and advanced stages as an aid to interpretation. The appearance of each stage has been described and illustrated with photographs and diagrammatic drawings as well as by a comparison of each stage with its corresponding pathologic picture.

Protein Studies in Atrophic and Hypertrophic Arthritis.—Davis' [17] studies show that globulin (especially the euglobulin fraction) and usuall fibrinogen tend to increase and albumin tends to decrease in rheumatoid arthritis (atrophic), whereas there is little or no change in the protein fraction in osteo-arthritis (hypertrophic). This tends to show that rheumatoid arthritis is an infectious disease, while osteo-arthritis is not. The sedimentation index is a simple way of determining the globulin content.

NEOPLASMS

Vertebral Angioma.—Lamy and Weissman [18] discuss this disease in the light of about 20 cases that have been discovered since 1926, when the condition was first recognized. The occurrence of vertebral angioma (or hemangioma) is more common than the short time that it has been

15. Golding, F. C.: Brit. J. Surg. **23**:484, 1936.
16. Spackman, E. W.: Am. J. Roentgenol. **35**:156, 1936.
17. Davis, J. S.: J. Lab. & Clin. Med. **21**:478, 1936.
18. Lamy, L., and Weissman, L.: Rev. d'orthop. **23**:121, 1936.

recognized would lead one to believe. Schmorl found it to be present in 10 per cent of about 10,000 spines that he examined, and other autopsy statistics have agreed with his figures. Essentially a benign tumor, it has rarely been discovered clinically. Angioma without symptoms seems to occur in elderly people, while angioma with symptoms occurs in persons from 20 to 25. The dorsal portion of the spine is most often involved, and the cervical portion, rarely. More than one vertebra may be affected. The only pathogenic finding of note is the frequent occurrence of other angiomas in the skin, liver, spleen, etc. There are two types of symptoms: motor or sensory, the former being more common. Diagnosis is impossible without roentgenograms. So far as the sensory symptoms are concerned, rest, support and roentgen therapy secure excellent results. When paraplegia is present, more radical treatment is necessary, unless the disease is allowed to run on to a fatal end. Laminectomy followed by radiation is the treatment of choice, with, however, no more than 50 per cent chance of cure. Laminectomy is extremely difficult, and half the persons operated on died of hemorrhage.

Hodgkin's Disease of Bone.—Morrison [19] feels that Hodgkin's disease is a loose diagnostic term for a number of hematogenous tumor growths. The osseous system is involved in from 10 to 50 per cent of the cases. Four types of bony involvement are recognized: (1) pressure erosion, e. g., an enlarging lymph node; (2) granulomatous periostitis, by direct extension from surrounding tissues; (3) invasion of the medullary cavity, and (4) osseous hyperplasia. Often there are no clinical signs, and Hodgkin's disease in bone is found only by roentgenograms. The changes shown in the roentgenograms frequently resemble carcinomatous metastases. In rare instances Hodgkin's disease may begin primarily in the bone. Three personally observed cases are reported in detail.

ISCHEMIC AND SPASTIC PARALYSIS

Ischemic Contracture.—Steindler [20] reports 50 cases of fracture at the elbow complicated by Volkmann's ischemic contracture from his own clinic, in 43 of which treatment was given. Eleven of the patients were treated conservatively, i. e., by means of stretching, splints and physical therapy, while the remaining 32 were treated with combined conservative and operative measures. The operations used were myotomy of the pronator muscles (4 cases), epicondylar stripping (5 cases), transplantation of tendons (4 cases), plastic lengthening of the flexor tendons (27 cases), resection of the radius and ulna (1 case), resection of the metacarpal heads (1 case), neurolysis (2 cases) and

19. Morrison, M. C.: Canad. M. A. J. **34**:393, 1936.
20. Steindler, A.: Surg., Gynec. & Obst. **62**:358, 1936.

transplantation of the ulnar nerve (2 cases). The author emphasizes the necessity of prolonged conservative treatment in each case. He reviews the clinical and experimental data on the cause and pathologic process of ischemic contracture, emphasizing the importance of prompt reduction of the fracture and maintenance of the reduction, but he points out that ischemic contracture can and does develop in spite of complete immediate reduction. He stresses the importance of careful observation of the first signs of ischemia, which are: edema, cyanosis, pain, paresthesia, hyperesthesia, motor paralysis and trophic disturbances. With the appearance of any of these signs, the dressing should be removed and the arm placed in the position of greatest comfort, usually in partial extension, for forty-eight hours.

Volkmann's Contracture.—Meyerding [21] reports 69 cases of Volkmann's contracture following supracondylar fracture of the humerus. The condition in most cases was a late result, the original fracture being in some other location. In the acute stage Meyerding recommends elevation of the arm on pillows or an airplane splint. Drainage of large hematomas may be indicated. Immediate open reduction may be used in selected cases. The late results are treated primarily by conservative measures, such as were advocated by Sir Robert Jones. Operations, such as tendon lengthening manipulation, neurolysis, bone resection, etc., were performed in 33 cases.

The Spastic Child.—In an excellently written article, Brockway [22] presents the results of the study of 1,000 patients with cerebral birth hemorrhage who were treated at the Orthopaedic Hospital in Los Angeles. In 39 per cent of the cases there was a history of difficult labor. The rôle of the orthopedic surgeon in the care of such patients is stressed, but Brockway feels that there should be a medical, dental, neurosurgical and psychologic consultation in each case. If the intelligence rating is 80 or above, the prognosis for improvement under treatment is excellent. Physical therapy, braces and operative procedures, particularly tenotomy, neurectomy, and stabilization of the feet, are more commonly done. The vocational, social and economic sides of the patient's life are important.

OSTEOCHONDRITIS

Osteochondritis Dissecans as Related to Trauma.—Funston and Kinser [23] report 23 cases of osteochondritis dissecans. Of this series, the carpal scaphoid bone was involved in 1 case, the carpal semilunar

21. Meyerding, H. W.: Volkmann's Ischemic Contracture Associated with Supracondylar Fracture of the Humerus, J. A. M. A. **106**:1139 (April 4) 1936.

22. Brockway, A.: Problem of the Spastic Child, with Clinical Summary of One Thousand Cases, J. A. M. A. **106**:1635 (May 9) 1936.

23. Funston, R. V., and Kinser, P.: South. M. J. **29**:262, 1936.

bone in 1, the acetabulum bilaterally in 1, the patellae in 3, in 1 of which the involvement was bilateral, the astragalus in 1, the head of the femur bilaterally in 1, a vertebra bilaterally in 1, the condyles of the femur in 6, the lower end of the tibia in 1 and the upper end of the tibia in 1. It is the impression of the authors that trauma is the chief etiologic factor. Operation was performed in 9 of these cases.

[ED. NOTE.—The question arises whether some of the patients may not have had definite fractures not recognized at the time of injury. There are many similarities between fractures of the articular surfaces and the so-called osteochondritis dissecans as seen ordinarily.]

Articular Lesions Following Work with Compressed Air Tools.—Rostock [24] studied 290 patients suffering from articular lesions resulting from work with compressed air tools. The elbow joint was involved in 240 cases, the hand in 44 and the shoulder in 3. In general, two types of major injury are to be observed. One is due to muscle and tendon pull and results in exostosis. The other type involves the joints and results in either osteochondritis dissecans or general changes in the joint surfaces. At the elbow, olecranon spurs at the point of the attachment of the triceps muscle are ten times as common in miners as in ordinary workers. A ringed circle of osteophytes often outlines the head of the radius. The typical exostosis is at the site of origin of the brachialis anticus muscle on the humerus. In the early stages it has the appearance of myositis ossificans. Later the outlines become distinct and free bodies form. When articular changes are pronounced, they may be found in association with a grotesque bony mass in the brachialis anticus muscle. In the hand changes occur in the lunate and navicular bones; necrosis of the lunate bone and pseudarthrosis of the navicular bone appear. At the shoulder, changes in form are found in association with marginal osteophytes. Subchondral necrosis underlies these alterations. Changes similar to those seen in compressed air workers occur in stone masons, locomotive firemen and other laborers. Localized lesions are sometimes seen in athletes.

MISCELLANEOUS

"Well Leg Traction" in Correcting Orthopedic Deformities.—White [25] reviews the use of "well leg traction" in the treatment of many types of lesions of the bones and joints of the legs. He believes that a form of traction applied with a device easily constructed by means of plaster of paris and an ordinary shelf or wall-bracket is superior to weight and pulley traction because of the fixed nature of the apparatus and the lessened need for adjustment. When considerable force is

24. Rostock, P.: Med. Klin. **32**:341, 1936.
25. White, J. W.: South. M. J. **29**:45, 1936.

required over a relatively short period, a Steinmann pin is used in the affected leg. In treating lesions such as contractures, tuberculous joints, unreduced dislocation of the hip and postoperative lesions about the hip, skin traction suffices. The use of well leg traction is mentioned in such cases as correction of lumbar scoliosis and, in a reversed manner, to obtain firm apposition after arthrodesis of the knee.

Traumatic Arterial Thrombosis of the Forearm.—Schär and Neff [26] call attention to the syndrome of traumatic peripheral arterial thrombosis. The case history and the histologic section of the affected artery in each of 2 cases are reported. In the first, after forced dorsiflexion of the wrist, pain appeared in the region of the flexor muscles at the wrist. The wrist was immobilized and improved rapidly. However, commencing two weeks after the injury there appeared a tender long mass deep over the region of the ulnar artery. At the same time pain began to radiate to the tips of the third, fourth and fifth fingers. At operation a thrombosed ulnar artery was found adherent to the ulnar nerve. An old thrombus adherent to one area of the arterial wall was found where the intima and the elastic layer had ruptured. Cure followed excision of the thrombosed segment. In the second case the ramus volaris superficialis of the radial artery was affected after a blow in the snuff box area. In each instance, after an initial period of pain, a period of freedom from pain appeared. Then there followed an episode of radiating pain in the nerve due to adherence of the thrombosed inflamed vessel, which persisted until excision.

Therapy of Aseptic Necrosis.—Lauber and Löber,[27] in cases of malacia of the semilunar bone following injuries, found that of 12 cases in which extirpation of the semilunar bone had been performed, the results were satisfactory in only 2. The rest of the patients for the most part had severe pain, which interfered with their occupation. In 6 cases in which operation was not performed the results were better on the whole than in the average case in which operation was performed. Arthritic alterations and restriction of motion at the wrist were regularly found, however. The authors stated that in malacia of the tarsal scaphoid bone and the head of the second metatarsal bone, conservative treatment gave excellent results.

PATHOLOGY

Regeneration of Muscular Fibers After Injury.—Schmincke [28] describes the regeneration of muscle fibers as occurring in two ways.

26. Schär, W., and Neff, G.: Deutsche Ztschr. f. Chir. **246**:95, 1936.

27. Lauber, H. J., and Löber, H. J. A.: Deutsche Ztschr. f. Chir. **246**:366, 1936.

28. Schmincke, A.: Med. Klin. **32**:475, 1936.

In one, true regeneration occurs. New fibers are built from old by a flowing of homogeneous sarcoplasmic processes of irregular form. Into these processes sarcolemmic nuclei grow. Secondary changes then occur: first longitudinal and then cross striations appear. In most cases fibrils develop which connect with the fibrils in the old fibers. In the second type of regeneration development is of a discontinuous, rather embryonal type. Young muscle fiber cells of spindle shape appear near each other. The plasma boundaries disappear, longitudinal and transverse striations appear in the fused sarcoplasm and a sarcolemma is formed, to complete the new fibers. Why one or the other type of regeneration will appear in a given muscle injury is not known. Some believe that the embryonal type is the more complete type of repair and occurs when more of the sarcolemma structure is retained, as in infectious myositis (destruction of the rectus muscle in typhoid, for example). In most cases in human beings the first type of attempted repair takes place. However, the connective tissue elements may grow around the sarcolemmic processes, rendering the repair abortive, and finally result in a mass or scar tissue with no true muscle function.

ORTHOPEDIC OPERATIONS

Election of Site of Amputation in Diabetic Gangrene.—Matyas [29] does not agree to high amputation in the presence of diabetic gangrene. He states that the site of election is low, from 3 to 4 fingerbreadths above the uppermost level of gangrenous demarcation. Operation is performed without the use of a tourniquet, and consequently bleeding serves as the major corroborative evidence of the correctness of the site of amputation. Bleeding is usually free in persons with diabetes. If it is not free, arteriosclerosis is usually present and necessitates amputation higher on the limb. According to Matyas, this conservative attitude has saved limb-length and is justified in his experience. Specific antidiabetic medication, of course, precedes amputation. Three cases are reported in detail. Indications for amputaton are made early and are as follows: (1) fever, (2) general condition and (3) local findings. The muscles and fascial flap are left long without suture. The author states that muscles and fascia do poorly in persons with diabetes when sutured.

Rupture of Long Head of Biceps Brachialis Muscle.—In reporting 4 cases of rupture of the long head of the biceps brachialis muscle, Harris [30] describes the operation of Trethewan. This consists of suturing the torn tendon of the long head to the coracoid process of the scapula after passing it through the short head of the biceps muscle.

29. Matyas, M.: Arch. f. klin. Chir. **184**:624, 1936.
30. Harris, H. A. H.: Brit. J. Surg. **23**:572, 1936.

End-Results of Excision of Elbow.—Bugby [31] reported the results of excision of the elbow in 15 instances. They were successful in 12 cases, and in all of these good power in flexion and complete extension were obtained. For a number of months after operation there was considerable lateral instability of the joint, but this grew less. Bugby feels that excision is often preferable to arthroplasty. In his cases the operation was done for tuberculosis, traumatic ankylosis, old compound fractures and osteomyelitis as a complication of typhoid.

Arthroplasty in Ankylosis Following Gonorrheal Arthritis.—Essbach,[32] working in the clinic of E. Payr, reports the results of arthroplasty in 28 patients with gonorrheal arthritis. In 4, a preliminary operation alone was carried out, but arthroplasty was not attempted. In the remaining 24 the results were good in 18, in 4 the operation was a failure and 2 of the patients were not examined. A gonorrheal joint, if absolutely quiescent, is ideal for the operation. The presence of any local tenderness, a relative lymphocytosis, chronic ascending genital gonorrhea in the female and polyarthritis are usually contraindications for arthroplasty. The operation should not be performed on the aged or in cases in which the limb will be subjected to excessive strain.

End-Results of Leg Lengthening.—Stephenson and Durham [33] report 17 cases of leg lengthening, 15 of the tibia and fibula and 2 of the femur, in children over 12 years of age. In no case was the operation a failure. Lengthening varied from 1¾ to 2¾ inches (2.4 to 6.9 cm.), and in 1 case the femur was lengthened 3¼ inches (8.2 cm.). All patients were up and wearing casts in three months. The bones were regenerated in all cases in from six to eight months. Strict operative asepsis, careful roentgenographic control of the fragments and care in the selection of the patients are stressed. The apparatus used was of the modified Abbott type.

Synovectomy of the Knee Joint in Chronic Arthritis.—David [34] reports the results following 11 synovectomies of the knee on 10 patients. Eight had good functional results without pain. The author stresses the value of this operation. It is contraindicated in the presence of active infection, tuberculosis and in uncooperative patients. Prior to operation, foci of infection and mechanical abnormalities are cared for.

[ED. NOTE.—In well selected cases this operation is one of the greatest value. It is more successful in the knee joint, however, than

31. Bugby, B. F.: Ann. Surg. **103**:625, 1936.

32. Essbach, H.: Deutsche Ztschr. f. Chir. **246**:256, 1936.

33. Stephenson, G. B., and Durham, H. A.: South. M. J. **28**:818, 1935.

34. David, S. D.: South. M. J. **28**:867, 1935.

in other joints. When operation is not feasible, a similar result can often be obtained by prolonged roentgen therapy.]

Derotation of the Tibia.—Stirling [35] describes a method of "derotating" the tibia which consists essentially of making a subperiosteal incomplete oblique fracture by a series of drill holes. He found it was of particular value in cases of malunion of tibial fractures when the vascularity of the bone was not normal.

Arthrodesis of the Foot.—The results of 17 bone block operations on the ankle joint are discussed by Sorrel.[36] Ten posterior bone block operations were done by the method of Nové-Josserand (a long turned-up graft from the os calcis) combined with subastragalar and midtarsal arthrodesis. The operation was successful in all cases, and there was considerable hypertrophy of the posterior block of bone. In 1 case there was pseudarthrosis between the block of bone and the os calcis, but this did not interfere with the functional result. The conclusion was that this type of bone block was most successful but should be combined with subastragalar and midtarsal arthrodesis. Five anterior bone block operations were done after the method of Putti and 2 by means of an oblique graft running down from the anterior astragalus into the os calcis. The first was considered the best method as it could be employed in young children without arthrodesis of the subastragalar joint. All 5 of the bone block operations by the method of Putti were successful, while only 1 of the two transfixion grafts were successful.

Posterior Bone Block of the Ankle Joint.—Hackenbrock,[37] of Cologne, reviewed the results in 15 patients on whom a posterior bone block of the ankle joint had been performed. The methods of Campbell, or Nové-Josserand, and of Camera had been used. In all these patients the operation sought to correct a foot drop, which was the result of infantile paralysis. The author found functional improvement in all of these patients, except 1, who was not yet walking after the operation. He advises that posterior bone block be combined with subastragalar arthrodesis.

Surgical Treatment of Syringomyelia.—Frazier and Rowe [38] discuss the surgical treatment of syringomyelia and report 2 cases in which surgical drainage of the cystic cavities in the spinal cord was successfully carried out. They make the point of attempting to establish permanent surgical drainage by inserting a silk thread or a gutta-percha

35. Stirling, R. I.: Brit. M. J. **1**:58, 1936.

36. Sorrel, E.: Rev. d'orthop. **23**:193, 1936.

37. Hackenbrock, M.: Ztschr. f. orthop. Chir. **64**:222, 1936.

38. Frazier, C. H., and Rowe, S. N.: Ann. Surg. **103**:481, 1936.

drain. Roentgen therapy is stated to have been effective in certain cases reported in the literature. Frazier and Rowe feel that such treatment is indicated in dealing with gliosis and conclude that probably a combination of surgical and roentgen therapy may be a better approach than one or the other alone.

FRACTURES AND DISLOCATIONS

Compression Fractures of Spine.—An ingenious method of modifying an ordinary Simmons-Fowler bed is described by Morrison and Flamson [39] whereby fractures of the dorsal and lumbar portions of the spine may be satisfactorily hyperextended. Two changes are made in the bed—the head end of the spring section is fastened to the frame and the center or immobile section is loosened from the frame. By fixing the center and the lower section with steel strips, on cranking up the bed a simple angulation occurs.

[ED. NOTE.—For exact information regarding the modification of the bed, we suggest referring to this article, which contains illustrations.]

Fractures of the Lateral Condyle of the Humerus.—Wilson [40] found that fractures of the lateral condyle of the humerus in childhood occurred with a frequency of 2.5 per cent in 439 fractures and dislocations of the elbow. He states that the fracture is frequently not properly evaluated and that treatment is poorly conceived. The mechanism of injury and the pathologic process are described. When there are complete rotation and displacement of the fractured condyle, the articular surface faces upward, and nonunion will result unless the fragment is derotated and the opposing fracture surfaces are held together. The late complications from cases in which treatment is unsatisfactory are cubitus valgus and palsy of the ulnar nerve, which can be treated by supracondylar osteotomy and transplantation of the ulnar nerve.

United Fractures of the Neck of the Femur.—McMurray [41] has performed the bifurcation operation 27 times for nonunion following fractures of the neck of the femur. The results were generally good, though no figures were given. The technic of the procedure is described. Oblique osteotomy is performed at the level of the lower border of the head of the femur. Osteotomy above or below the point may result in an unstable hip. Patients are left in a plaster cast in slight abduction for from three to four months afterward.

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39. Morrison, W. A., and Flamson, R. J.: California & West. Med. **43**:416, 1935.

40. Wilson, P. D.: J. Bone & Joint Surg. **18**:301, 1936.

41. McMurray, T. P.: J. Bone & Joint Surg. **18**:319, 1936.

Fractures of the Patella.—Partial or total excision of the patella is recommended by Blodgett and Fairchild [42] as the treatment of choice for acute fractures. If there is marked comminution, "subperiosteal excision" is done at once. If a sizable distal fragment is present, it is preserved, and the proximal fragments only are excised. The authors believe that the period of hospitalization is shortened and that the functional results are at least as good as in the older methods of open reduction and suture. The excised portion does not regenerate. They stress the necessity of outline of the torn joint capsule. Of 20 cases in which partial or total excision was carried out, the results were excellent in 7, good in 4 and unknown in 9.

Fractures of the Neck of the Femur.—Galland [43] has had excellent results in the treatment of ununited fracture of the neck of the femur following the use of the Lorenz bifurcation operation. In 6 patients, painters, stable weight-bearing hips were obtained after this procedure. Only a slight to moderate limp remained, and the patients were able to resume practically normal activity. The author describes in detail the mechanics and operation technic of the method.

Dislocation of the Head of the Fibula in Sports.—Strauss [44] reports the occurrence of sudden pain in the knee and weakness in a 7 year old girl during play. No effusion appeared in the knee joint. The head of the fibula was tender. A roentgenogram revealed anterior displacement of the head of the fibula. Reduction with the patient under anesthesia followed by immobilization in extension in a cast resulted in complete recovery. The author reviews the literature of this interesting syndrome and discusses the mechanophysiology of the dislocation. It seems most likely that the actual dislocation occurs as the result of stresses transmitted up through the fibula at the moment of impact with the ground. Not until the ligaments of the tibia and fibula are torn by lever action does dislocation occur through muscular pull. The muscles involved are mainly the extensor digitorum communis, the extensor hallucis longus and the biceps femoris muscle. The prognosis is good. No lasting peroneal palsy has been reported. Despite the fact that between 15 and 20 per cent of cadavers show communication between the tibiofibular and the tibiofemoral joint, no effusion is observed in the joint.

Dislocation of the Base of the Fifth Metacarpal Bone.—Roberts and Holland [45] describe 4 cases of isolated dislocation of the base of

42. Blodgett, W. E., and Fairchild, R. D.: Fractures of the Patella: Results of Total and Partial Excisions of the Patella for Acute Fracture, J. A. M. A. **106**:2121 (June 20) 1936.

43. Galland, W. I.: Surg., Gynec. & Obst. **30**:410, 1935.

44. Strauss, F.: Deutsche Ztschr. f. Chir. **246**:212, 1936.

45. Roberts, N., and Holland, C. I.: Brit. J. Surg. **23**:567, 1936.

the fifth metacarpal bone. In 3 of these the base was displaced slightly inward and forward; in the fourth the base was displaced forward and outward so as to lie in the palm in front of the bases of the third and fourth metacarpal bones. Open reduction was necessary in the last case.

Arrest of Growth After Fractures into the Epiphyses.—In a study of fractures occurring in children 14 years of age or younger, Compere [46] found that in 14 per cent an epiphysis was involved. Of 19 cases in which the epiphysial line was involved in the fracture, growth disturbances of various degrees were found in 18 on careful follow-up study. Compere advises that patients with fracture involving the epiphysial line be followed through the growth period and that the prognosis be guarded.

RESEARCH

Attempts to Produce Paget's Disease by Pituitary and Parathyroid Extracts.—Believing that the pituitary gland and the parathyroid glands are important factors in the development of bone, Moehling and his co-workers [47] administered anterior pituitary extract and parathyroid extract to 7 adult dogs. The animals were followed by studies of blood chemistry, roentgenograms and necropsy. No changes in the bone simulating Paget's disease were noted, but there was deposition or replacement of bone marrow by calcium in the dogs receiving the pituitary and the parathyroid extracts, but none in those receiving parathyroid extract alone. Three of the dogs showed renal deposits of calcium. Various other changes in the tissues were noted, such as excessive ovulation and alterations in the thyroid gland.

Tensile Strength of Human Tendons.—Cronkite [48] states that it is generally accepted that normal tendons are never ruptured by intrinsic or extrinsic tension but are evulsed from the muscular tissue to which they are attached. Experiments were carried out to determine the tensile strength in pounds per square inch for the various undiseased tendons. The strength varied from 4,000 to 30,000 pounds per square inch. The strength of fresh tendons did not differ much in strength from the fixed tendons secured from cadavers.

Callus Formation in the Presence of Foreign Bodies.—Koelsch [49] osteotomized the fibulas of rabbits and sutured the fragments with silk, catgut or Krupp steel wire. Comparisons of these with "normal" bones

46. Compere, E. L.: Growth Arrest in Long Bones as the Result of Fractures that Include the Epiphysis, J. A. M. A. **105**:2141 (Dec. 28) 1935.

47. Moehling, R. C.; Murphy, J. M., and Reynolds, L.: Am. J. Roentgenol. **34**:465, 1935.

48. Cronkite, A. E.: Am. J. Physiol. **64**:173, 1936.

49. Koelsch, K. A.: Deutsche Ztschr. f. Chir. **246**:642, 1936.

revealed that stainless steel wire interfered least with the formation, appearance and quantity of the callus formed.

Thermotherapy for Articular Disease.—Pattrinieri and Logroscino [50] report extensive experimental studies on animals of the effects of increased temperature of the tissues as produced by diathermy and the hot air method of Bier. In animals temperatures was carefully measured with the subject under anesthesia. Similar, but necessarily less complete, studies were made on human beings. The authors conclude that Bier's hot air method of producing heat is less dangerous, is less painful at higher temperatures and produces more satisfactory hyperemia and a higher temperature in the superficial as well as in the deep tissues. This extensive study includes observations on the reaction of the pulse, blood pressure, respiration, motor functions and mind. The effect on various tissues is noted. Definite increased temperature is noted in joints when the hot air bath is applied externally.

[Ed. Note.—This long and thorough article is incapable of brief abstraction and is recommended to those interested in the effects of the external application of heat.]

Effect of Immobilization on Normal Joint.—Experiments were carried out on dogs by Scogliette and Casuscion [51] to observe the articular changes following immobilization of the knee. The immobilization was carried out for periods varying from three to twelve months. Gross and microscopic examinations were made of the joints, and the following changes were noted: 1. A primary alteration of the synovial membrane, consisting of proliferation of the superficial layers, followed successively by endothelial desquamation with retraction of the villi and atrophy of the synovial membrane with consequent diminution of secretion of the synovial fluid, was observed. A little later sclerosis of the subserous tissue was seen. 2. A second period, a little later, was accompanied by alteration of the cartilage, that is, death of the "baso-philia," irregularity of formation of the cartilaginous sheath, diminution of its thickness and the formation of defects. The alteration of the cartilage was caused by the lack of functional stimulation and the progressive diminution of the synovial fluid. 3. In consequence of immobilization of a normal joint, the atrophy of inactivity involves all of its component parts, the synovial membrane, the cartilage and the bone.

[Ed. Note.—This article contains excellent colored photographs and photomicrographs. The sequence of events following immobilization of a joint is of great interest and importance.]

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50. Pattrinieri, M., and Logroscino, D.: Chir. d. org. di movimento **21**:303, 1936.

51. Scogliette, O., and Casuscion, C.: Chir. d. org. di movimento **21**:469, 1936.